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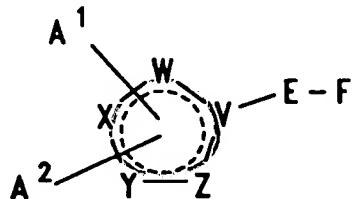
501 IMIDAZOLE, TRIAZOLE AND TETRAZOLE DERIVATIVES

5 The present invention relates to a class of substituted imidazole, triazole and tetrazole derivatives which act on 5-hydroxytryptamine (5-HT) receptors, being selective agonists of so-called "5-HT<sub>1</sub>-like" receptors. They are therefore useful in the treatment of clinical conditions for which a selective agonist of these receptors is indicated.

10 5-HT<sub>1</sub>-like receptor agonists which exhibit selective vasoconstrictor activity have recently been described as being of use in the treatment of migraine (see, for example, A. Doenicke *et al.*, The Lancet, 1988, 14 Vol. 1, 1309-11). The compounds of the present 15 invention, being selective 5-HT<sub>1</sub>-like receptor agonists, are accordingly of particular use in the treatment of migraine and associated conditions, e.g. cluster headache, chronic paroxysmal hemicrania, headache associated with vascular disorders, tension headache and paediatric migraine.

20 EP-A-0313397 describes a class of tryptamine derivatives substituted by a five-membered heteroaliphatic ring, which are stated to be specific to a particular type of "5-HT<sub>1</sub>-like" receptor and thus to be 25 effective therapeutic agents for the treatment of clinical conditions, particularly migraine, requiring this activity. However, EP-A-0313397 neither discloses nor suggests the imidazole, triazole and tetrazole derivatives provided by the present invention.

30 The present invention provides a compound of formula I, or a salt or prodrug thereof:



(1)

PS wherein the broken circle represents two non-adjacent  
 10 double bonds in any position in the five-membered ring;

P two, three or four of V, W, X, Y and Z  
 represent nitrogen and the remainder represent carbon  
 provided that, when two of V, W, X, Y and Z represent  
 nitrogen and the remainder represent carbon, then the  
 15 said nitrogen atoms are in non-adjacent positions within  
 the five-membered ring;

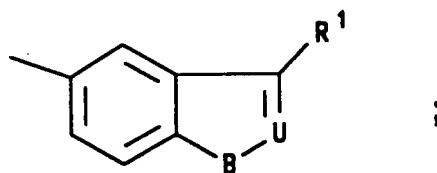
P A<sup>1</sup> represents hydrogen, hydrocarbon, a  
 heterocyclic group, halogen, cyano, trifluoromethyl,  
 13 -OR<sup>X</sup>, -SR<sup>X</sup>, -NR<sup>X</sup>RY, -NR<sup>X</sup>CORY, -NR<sup>X</sup>CO<sub>2</sub>RY, -NR<sup>X</sup>SO<sub>2</sub>RY, or  
 20 L -NR<sup>Z</sup>CTN<sup>X</sup>RY;

P A<sup>2</sup> represents a non-bonded electron pair when  
 four of V, W, X, Y and Z represent nitrogen and the other  
 represents carbon; or, when two or three of V, W, X, Y  
 and Z represent nitrogen and the remainder represent  
 25 carbon, A<sup>2</sup> represents hydrogen, hydrocarbon, a  
 heterocyclic group, halogen, cyano, trifluoromethyl,  
 -OR<sup>X</sup>, -SR<sup>X</sup>, -NR<sup>X</sup>RY, -NR<sup>X</sup>CORY, -NR<sup>X</sup>CO<sub>2</sub>RY, -NR<sup>X</sup>SO<sub>2</sub>RY, or  
 13 L -NR<sup>Z</sup>CTN<sup>X</sup>RY;

P E represents a bond or a straight or branched  
 30 alkylene chain containing from 1 to 4 carbon atoms;

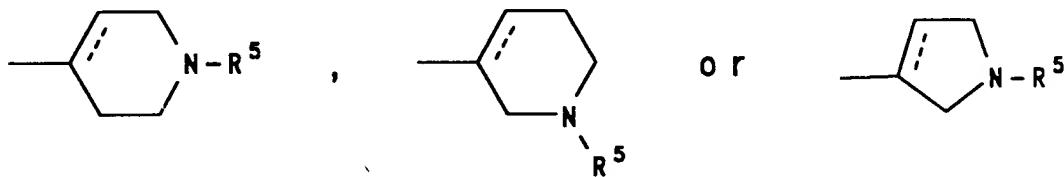
P F represents a group of formula

T40X



10       $\rho$       13      U represents nitrogen or C-R<sup>2</sup>;  
            |      |  
            B      U      B represents oxygen, sulphur or N-R<sup>3</sup>;  
formula      R<sup>1</sup> represents -CH<sub>2</sub>.CHR<sup>4</sup>.NR<sup>6</sup>R<sup>7</sup> or a group of

T41X



PS in which the broken line represents an optional chemical bond;

25       $\rho$       R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup> and R<sup>7</sup> independently represent hydrogen or C<sub>1-6</sub> alkyl;

25       $\rho$       R<sup>x</sup> and R<sup>y</sup> independently represent hydrogen, hydrocarbon or a heterocyclic group, or R<sup>x</sup> and R<sup>y</sup> together represent a C<sub>2-6</sub> alkylene group;

25       $\rho$       R<sup>z</sup> represents hydrogen, hydrocarbon or a heterocyclic group;

30       $\rho$       T represents oxygen, sulphur or a group of

50 formula =N.G; and

25       $\rho$       G represents hydrocarbon, a heterocyclic group or an electron-withdrawing group.

P The present invention also provides compounds of formula I above wherein three or four of V, W, X, Y and Z represent nitrogen and the remainder represent carbon;

5 P A<sup>2</sup> represents a non-bonded electron pair when four of V, W, X, Y and Z represent nitrogen and the other represents carbon; or, when three of V, W, X, Y and Z represent nitrogen and the remainder represent carbon, A<sup>2</sup> represents hydrogen, hydrocarbon, a heterocyclic group,

10 13 halogen, cyano, trifluoromethyl, -OR<sup>X</sup>, -SR<sup>X</sup>, -NR<sup>X</sup>RY,

L -NR<sup>X</sup>CORY, -NR<sup>X</sup>CO<sub>2</sub>RY, -NR<sup>X</sup>SO<sub>2</sub>RY, or -NR<sup>Z</sup>CTNR<sup>X</sup>RY; and

P A<sup>1</sup>, E, F, R<sup>X</sup>, R<sup>Y</sup>, R<sup>Z</sup> and T are as defined above.

L For use in medicine, the salts of the compounds of formula I will be non-toxic pharmaceutically acceptable salts. Other salts may, however, be useful in the preparation of the compounds according to the invention or of their non-toxic pharmaceutically acceptable salts. Suitable pharmaceutically acceptable salts of the compounds of this invention include acid addition salts which may, for example, be formed by mixing a solution of the compound according to the invention with a solution of a pharmaceutically acceptable non-toxic acid such as hydrochloric acid, fumaric acid, maleic acid, succinic acid, acetic acid, 15 benzoic acid, oxalic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid. Furthermore, where the compounds of the invention carry an acidic moiety, suitable pharmaceutically acceptable salts thereof may include alkali metal salts, e.g. sodium or potassium salts; alkaline earth metal salts, e.g. calcium or magnesium salts; and salts formed with suitable organic ligands, e.g. quaternary ammonium salts.

The term "hydrocarbon" as used herein includes straight-chained, branched and cyclic groups containing

up to 18 carbon atoms, suitably up to 15 carbon atoms, and conveniently up to 12 carbon atoms. Suitable hydrocarbon groups include C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, C<sub>3-7</sub> cycloalkyl(C<sub>1-6</sub>)alkyl, aryl 5 and aryl(C<sub>1-6</sub>)alkyl.

The expression "a heterocyclic group" as used herein includes cyclic groups containing up to 18 carbon atoms and at least one heteroatom preferably selected from oxygen, nitrogen and sulphur. The heterocyclic group suitably contains up to 15 carbon atoms and conveniently up to 12 carbon atoms, and is preferably linked through carbon. Examples of suitable heterocyclic groups include C<sub>3-7</sub> heterocycloalkyl, C<sub>3-7</sub> heterocycloalkyl(C<sub>1-6</sub>)alkyl, heteroaryl and 10 heteroaryl(C<sub>1-6</sub>)alkyl groups. 15

Suitable alkyl groups include straight-chained and branched alkyl groups containing from 1 to 6 carbon atoms. Typical examples include methyl and ethyl groups, and straight-chained or branched propyl and butyl 20 groups. Particular alkyl groups are methyl, ethyl and t-butyl.

Suitable alkenyl groups include straight-chained and branched alkenyl groups containing from 2 to 6 carbon atoms. Typical examples include vinyl and allyl 25 groups.

Suitable alkynyl groups include straight-chained and branched alkynyl groups containing from 2 to 6 carbon atoms. Typical examples include ethynyl and propargyl groups.

Suitable cycloalkyl groups include groups containing from 3 to 7 carbon atoms. Particular cycloalkyl groups are cyclopropyl and cyclohexyl. 30

A particular aryl group is phenyl.

Particular aryl(C<sub>1</sub>-6)alkyl groups include benzyl, phenethyl and phenylpropyl.

Suitable heterocycloalkyl groups include azetidinyl, pyrrolidyl, piperidyl, piperazinyl and 5 morpholinyl groups.

Suitable heteroaryl groups include pyridyl, 10 quinolyl, isoquinolyl, pyridazinyl, pyrimidinyl, pyrazinyl, pyranyl, furyl, benzofuryl, dibenzofuryl, thienyl, benzthienyl, imidazolyl, oxadiazolyl and thiadiazolyl groups.

Particular heteroaryl(C<sub>1</sub>-6)alkyl groups include pyridylmethyl and pyrazinylmethyl.

The hydrocarbon and heterocyclic groups may in turn be optionally substituted by one or more groups 15 selected from C<sub>1</sub>-6 alkyl, adamantyl, phenyl, halogen, C<sub>1</sub>-6 haloalkyl, C<sub>1</sub>-6 aminoalkyl, trifluoromethyl, hydroxy, C<sub>1</sub>-6 alkoxy, aryloxy, keto, C<sub>1</sub>-3 alkylenedioxy, nitro, cyano, carboxy, C<sub>2</sub>-6 alkoxy carbonyl, C<sub>2</sub>-6 alkoxy carbonyl(C<sub>1</sub>-6)alkyl, 20 C<sub>2</sub>-6 alkylcarbonyloxy, arylcarbonyloxy, C<sub>2</sub>-6 alkylcarbonyl, arylcarbonyl, C<sub>1</sub>-6 alkylthio, C<sub>1</sub>-6 alkylsulphinyl, C<sub>1</sub>-6 alkylsulphonyl, arylsulphonyl, NR<sup>v</sup>R<sup>w</sup>, -NR<sup>v</sup>COR<sup>w</sup>, -NR<sup>v</sup>CO<sub>2</sub>R<sup>w</sup>, 13 -NR<sup>v</sup>SO<sub>2</sub>R<sup>w</sup>, -CH<sub>2</sub>NR<sup>v</sup>SO<sub>2</sub>R<sup>w</sup>, -NHCONR<sup>v</sup>R<sup>w</sup>, -CONR<sup>v</sup>R<sup>w</sup>, -SO<sub>2</sub>NR<sup>v</sup>R<sup>w</sup> and -CH<sub>2</sub>SO<sub>2</sub>NR<sup>v</sup>R<sup>w</sup>, in which R<sup>v</sup> and R<sup>w</sup> independently represent 25 hydrogen, C<sub>1</sub>-6 alkyl, aryl or aryl(C<sub>1</sub>-6)alkyl, or R<sup>v</sup> and R<sup>w</sup> together represent a C<sub>2</sub>-6 alkylene group.

When R<sup>x</sup> and R<sup>y</sup>, or R<sup>v</sup> and R<sup>w</sup>, together represent a C<sub>2</sub>-6 alkylene group, this group may be an ethylene, propylene, butylene, pentamethylene or hexamethylene group, preferably butylene or pentamethylene.

30 When the group G represents an electron-withdrawing group, this group is suitably cyano, nitro, 13 -COR<sup>x</sup>, -CO<sub>2</sub>R<sup>x</sup> or -SO<sub>2</sub>R<sup>x</sup>, in which R<sup>x</sup> is as defined above.

The term "halogen" as used herein includes fluorine, chlorine, bromine and iodine, especially fluorine.

The present invention includes within its scope 5 prodrugs of the compounds of formula I above. In general, such prodrugs will be functional derivatives of the compounds of formula I which are readily convertible in vivo into the required compound of formula I. Conventional procedures for the selection and preparation 10 of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

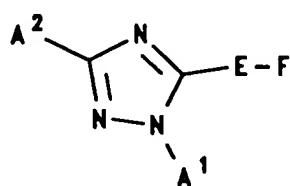
Where the compounds according to the invention have at least one asymmetric centre, they may accordingly 15 exist as enantiomers. Where the compounds according to the invention possess two or more asymmetric centres, they may additionally exist as diastereoisomers. It is to be understood that all such isomers and mixtures thereof are encompassed within the scope of the present 20 invention.

It will be appreciated that the imidazole, triazole and tetrazole rings of formula I can exist in a variety of canonical forms. These may suitably be represented by formulae IA to IT as follows:

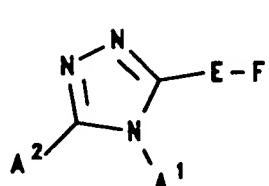
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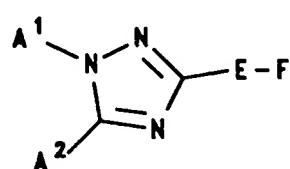
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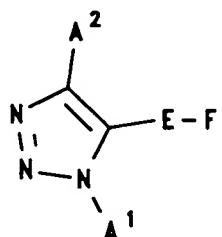
(IA)



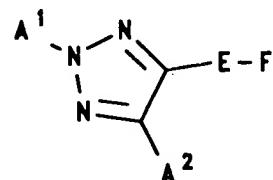
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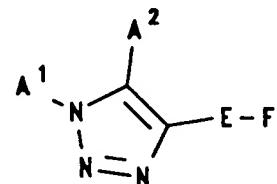
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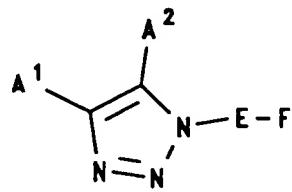
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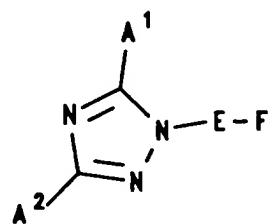
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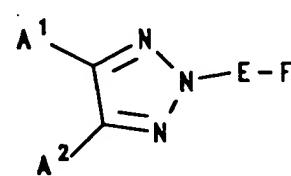
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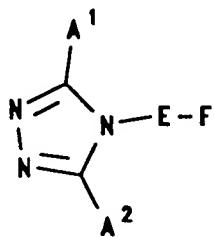
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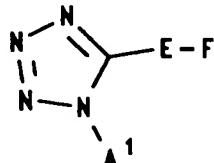
(IH)



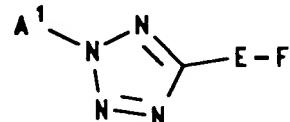
(IJ)



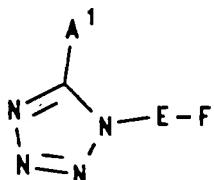
(I K)



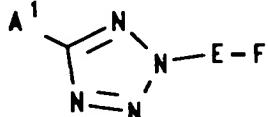
(I L)



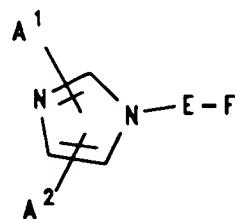
(I M)



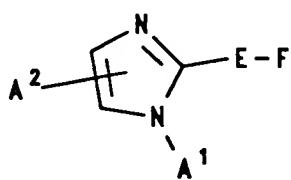
(I N)



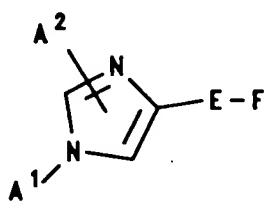
(I P)



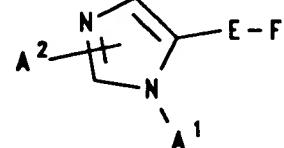
(I Q)



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(I T)

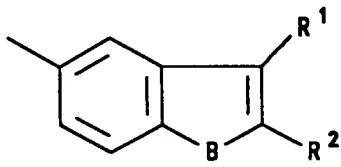
PS wherein A<sup>1</sup>, A<sup>2</sup>, E and F are as defined above. Preferred  
30 imidazole, triazole and tetrazole rings of formula I  
include the rings represented by formulae IA, IC, IG, IH,  
IL, IM, IN, IP and IQ above, especially IH.

P The alkylene chain E may be, for example,  
methylene, ethylene, 1-methylethylene, propylene or

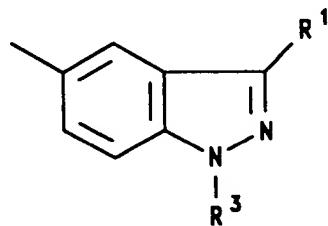
2-methylpropylene. Alternatively, the group E may represent a single bond such that the group F in formula I is attached directly to the five-membered heteroaromatic ring.

5 The group F is suitably an indole, benzofuran or benzthiophene moiety of formula FA, or an indazole moiety of formula FB:

T110X



(FA)



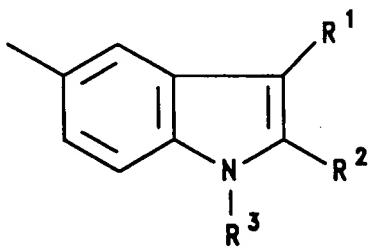
(FB)

PS

wherein B, R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above.

Preferably, the group F represents an indole moiety of structure FC:

T111X



(FC)

PS

wherein R<sup>1</sup>, R<sup>2</sup> and R<sup>3</sup> are as defined above, in particular wherein R<sup>2</sup> and R<sup>3</sup> are both hydrogen.

30 It will be appreciated that when four of V, W, X, Y and Z represent nitrogen and the other represents carbon, i.e. when the ring of formula I is a tetrazole ring, then the group A<sup>2</sup> will be a non-bonded electron pair. Otherwise, A<sup>1</sup> and A<sup>2</sup> will independently represent hydrogen, hydrocarbon, a heterocyclic group, halogen,

|3 cyano, trifluoromethyl, -OR<sup>x</sup>, -SR<sup>x</sup>, -NR<sup>x</sup>R<sup>y</sup>, -NR<sup>x</sup>COR<sup>y</sup>,  
L -NR<sup>x</sup>CO<sub>2</sub>R<sup>y</sup>, -NR<sup>x</sup>SO<sub>2</sub>R<sup>y</sup>, or -NR<sup>x</sup>CTNR<sup>x</sup>R<sup>y</sup>.

Suitable values for the groups A<sup>1</sup> and/or A<sup>2</sup> include C<sub>1-6</sub> alkyl, C<sub>3-7</sub> cycloalkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, 5 C<sub>3-7</sub> heterocycloalkyl, heteroaryl or heteroaryl(C<sub>1-6</sub>)alkyl, any of which groups may be optionally substituted; and hydrogen, halogen, cyano, trifluoromethyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio or -NR<sup>x</sup>R<sup>y</sup>, in which R<sup>x</sup> and R<sup>y</sup> are as defined above. Examples of optional substituents on the groups 10 A<sup>1</sup> and/or A<sup>2</sup> suitably include trifluoromethyl, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkoxy carbonyl, C<sub>2-6</sub> alkyl carbonyl, C<sub>1-6</sub> alkylsulphonyl, arylsulphonyl, amino, mono- or di(C<sub>1-6</sub>)alkylamino, C<sub>2-6</sub> alkyl carbonyl amino, aryl carbonyl amino, C<sub>2-6</sub> alkoxy carbonyl amino, C<sub>1-6</sub> alkylsulphonyl amino, 15 arylsulphonyl amino, C<sub>1-6</sub> alkylsulphonylaminomethyl, aminocarbonyl amino, mono- or di(C<sub>1-6</sub>)alkylaminocarbonyl amino, mono- or diarylaminocarbonyl amino, pyrrolidyl carbonyl amino, aminocarbonyl, mono- or di(C<sub>1-6</sub>)alkylaminocarbonyl, C<sub>1-6</sub> alkylaminosulphonyl, 20 aminosulphonylmethyl, and mono- or di(C<sub>1-6</sub>) - alkylaminosulphonylmethyl.

Particular values of A<sup>1</sup> and/or A<sup>2</sup> include hydrogen, methyl, methoxymethyl, aminomethyl, dimethylaminomethyl, acetylaminomethyl, 25 benzoylaminomethyl, t-butoxycarbonylaminomethyl, methylsulphonylaminomethyl, phenylsulphonylaminomethyl, aminocarbonylmethyl, ethyl, aminoethyl, acetyl aminoethyl, benzoyl aminoethyl, methoxycarbonyl aminoethyl, ethoxycarbonyl aminoethyl, t-butoxycarbonyl aminoethyl, 30 methylsulphonyl aminoethyl, aminocarbonyl aminoethyl, methylaminocarbonyl aminoethyl, t-butylaminocarbonyl aminoethyl, phenylaminocarbonyl aminoethyl, pyrrolidyl carbonyl aminoethyl, cyclopropyl, phenyl, methylsulphonylaminophenyl, aminocarbonylphenyl,

methylaminocarbonylphenyl, methylsulphonylaminomethylphenyl, aminosulphonylmethylphenyl, methylaminosulphonylmethylphenyl, dimethylaminosulphonylmethylphenyl, benzyl, trifluoromethylbenzyl, methoxybenzyl, acetylaminobenzyl,  
5      methylsulphonylaminobenzyl, aminocarbonylaminobenzyl, aminocarbonylbenzyl, methylaminocarbonylbenzyl, methylsulphonylbenzyl, methylaminosulphonylbenzyl, pyridylmethyl, methoxypyridylmethyl, amino, methylamino, benzylamino, dimethylamino, t-butoxycarbonylamino-  
10     ethylamino and methylsulphonylaminoethylamino.

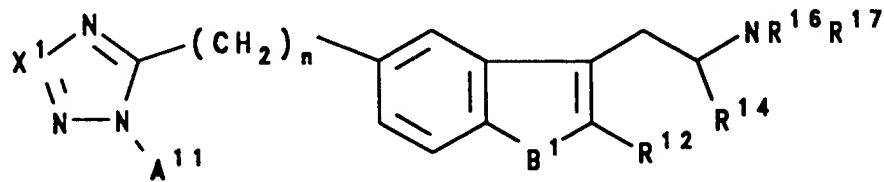
Preferred values of  $A^1$  and/or  $A^2$  include hydrogen, methyl, ethyl, benzyl and amino.

Representative values of  $R^1$  include aminoethyl, N-methylaminoethyl, N,N-dimethylaminoethyl, 4-piperidyl,  
15     1-methyl-4-piperidyl, 3-pyrrolidinyl and 1-methyl-3 $\Theta$  pyrrolidinyl.

Preferred values for the groups  $R^2$  to  $R^7$  are hydrogen and methyl.

A particular sub-class of compounds according  
20     to the invention is represented by the compounds of formula IIA, and salts and prodrugs thereof:

T130X



(IIA)

30 PS wherein

P 13  $X^1$  represents nitrogen or  $A^{12}$ -C;

  n is zero, 1, 2 or 3;

  P 13  $B^1$  represents oxygen, sulphur or  $N-R^{13}$ ;

ρ A<sup>11</sup> and A<sup>12</sup> independently represent C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, C<sub>3-7</sub> heterocycloalkyl, heteroaryl or heteroaryl(C<sub>1-6</sub>)alkyl, any of which groups may be 5 optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio or, -NR<sup>X</sup>R<sup>Y</sup>;

ρ R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>16</sup> and R<sup>17</sup> independently represent hydrogen or C<sub>1-6</sub> alkyl; and

ρ R<sup>X</sup> and R<sup>Y</sup> independently represent hydrogen, 10 hydrocarbon or a heterocyclic group, or R<sup>X</sup> and R<sup>Y</sup> together represent a C<sub>2-6</sub> alkylene group.

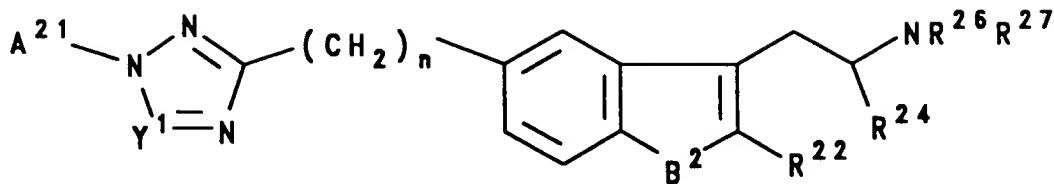
ρ Examples of optional substituents on the groups A<sup>11</sup> and A<sup>12</sup> suitably include trifluoromethyl, C<sub>1-6</sub> alkoxy, C<sub>2-6</sub> alkoxy carbonyl, C<sub>2-6</sub> alkyl carbonyl, C<sub>1-6</sub> alkylsulphonyl, 15 arylsulphonyl, amino, mono- or di(C<sub>1-6</sub>)alkylamino, C<sub>2-6</sub> alkyl carbonyl amino, aryl carbonyl amino, C<sub>2-6</sub> alkoxy carbonyl amino, C<sub>1-6</sub> alkylsulphonyl amino, arylsulphonyl amino, C<sub>1-6</sub> alkylsulphonyl amine methyl, aminocarbonyl amino, mono- or di(C<sub>1-6</sub>)alkylamino- 20 carbonyl amino, mono- or diarylaminocarbonyl amino, pyrrolidyl carbonyl amino, aminocarbonyl, mono- or di(C<sub>1-6</sub>)alkylaminocarbonyl, C<sub>1-6</sub> alkyl amine sulphonyl, aminosulphonyl methyl, and mono- or di(C<sub>1-6</sub>)alkyl- aminosulphonyl methyl.

ρ Particular values of A<sup>11</sup> and A<sup>12</sup> with respect to 25 formula IIA include hydrogen, methyl, ethyl, benzyl and amino. When X<sup>1</sup> represents A<sup>12</sup>-C, the group A<sup>11</sup> is 13 preferably hydrogen or methyl.

Preferably, R<sup>12</sup>, R<sup>13</sup> and R<sup>14</sup> each represents 30 hydrogen. Preferred values of R<sup>16</sup> and R<sup>17</sup> with respect to formula IIA include hydrogen and methyl.

Another sub-class of compounds according to the invention is represented by the compounds of formula IIB, and salts and prodrugs thereof:

T150X



(IIB)

10 PS wherein

P 13 Y<sup>1</sup> represents nitrogen or A<sup>22</sup>-C;

13 n is zero, 1, 2 or 3;

13 B<sup>2</sup> represents oxygen, sulphur or N-R<sup>23</sup>;

A<sup>21</sup> and A<sup>22</sup> independently represent C<sub>1-6</sub> alkyl,

15 C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, aryl, aryl(C<sub>1-6</sub>)alkyl, C<sub>3-7</sub> heterocycloalkyl, heteroaryl or heteroaryl(C<sub>1-6</sub>)alkyl, any of which groups may be optionally substituted; or hydrogen, halogen, cyano, trifluoromethyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio or -NR<sup>X</sup>R<sup>Y</sup>;

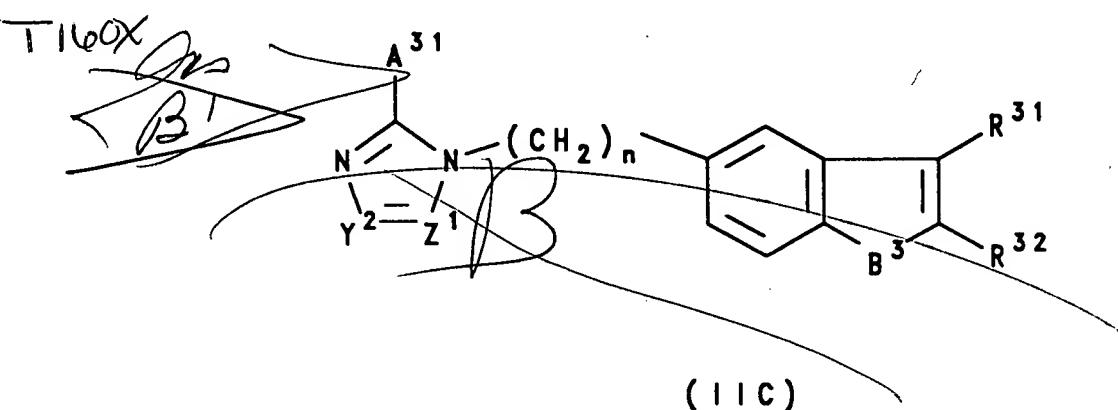
20 P R<sup>22</sup>, R<sup>23</sup>, R<sup>24</sup>, R<sup>26</sup> and R<sup>27</sup> independently represent hydrogen or C<sub>1-6</sub> alkyl; and

P R<sup>X</sup> and R<sup>Y</sup> independently represent hydrogen, hydrocarbon or a heterocyclic group, or R<sup>X</sup> and R<sup>Y</sup> together represent a C<sub>2-6</sub> alkylene group.

25 P Examples of optional substituents on the groups A<sup>21</sup> and A<sup>22</sup> correspond to those indicated for the groups A<sup>11</sup> and A<sup>12</sup> with respect to formula IIA above. Particular values of A<sup>21</sup> and A<sup>22</sup> with respect to formula IIB include hydrogen, methyl, ethyl and benzyl.

30 Preferably, R<sup>22</sup>, R<sup>23</sup> and R<sup>24</sup> each represents hydrogen. Preferred values of R<sup>26</sup> and R<sup>27</sup> with respect to formula IIB include hydrogen and methyl.

A further sub-class of compounds according to the invention is represented by the compounds of formula IIC, and salts and prodrugs thereof:



PS

wherein

15      P 13       $\gamma^2$  represents nitrogen or  $A^{32}-C$ ;  
             $Z^1$  represents nitrogen or CH;  
            n is zero, 1, 2 or 3;  
            13       $B^3$  represents oxygen, sulphur or  $N-R^{33}$ ;  
             $A^{31}$  and  $A^{32}$  independently represent  $C_{1-6}$  alkyl,  
             $C_{2-6}$  alkenyl,  $C_{2-6}$  alkynyl,  $C_{3-7}$  cycloalkyl, aryl,  
20      aryl( $C_{1-6}$ )alkyl,  $C_{3-7}$  heterocycloalkyl, heteroaryl or  
            heteroaryl( $C_{1-6}$ )alkyl, any of which groups may be  
            optionally substituted; or hydrogen, halogen, cyano,  
            trifluoromethyl,  $C_{1-6}$  alkoxy,  $C_{1-6}$  alkylthio or  $-NR^xR^y$ ;  
            P 13       $R^{31}$  represents  $-CH_2-CHR^{34}.NR^{36}R^{37}$  or a group of  
25      formula

T170X



10

$\rho$   $R^{32}$ ,  $R^{33}$ ,  $R^{34}$ ,  $R^{35}$ ,  $R^{36}$  and  $R^{37}$  independently represent hydrogen or C<sub>1-6</sub> alkyl; and

$\rho$   $R^x$  and  $R^y$  independently represent hydrogen, hydrocarbon or a heterocyclic group, or  $R^x$  and  $R^y$  together represent a C<sub>2-6</sub> alkylene group.

15

$\rho$  Examples of optional substituents on the groups  $A^{31}$  and  $A^{32}$  correspond to those indicated for the groups  $A^{11}$  and  $A^{12}$  with respect to formula IIIA above. Particular values of  $A^{31}$  and  $A^{32}$  with respect to formula IIC include hydrogen, methyl and amino.

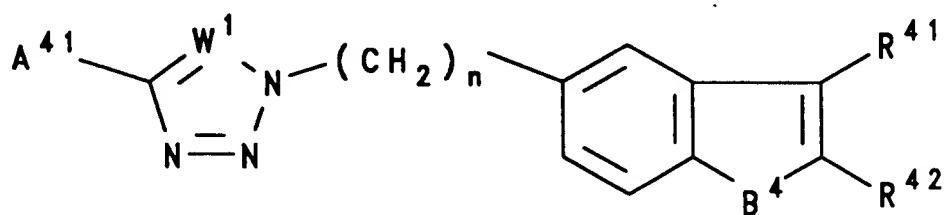
20

Preferably,  $R^{32}$ ,  $R^{33}$  and  $R^{34}$  each represents hydrogen. Preferred values of  $R^{35}$ ,  $R^{36}$  and  $R^{37}$  include hydrogen and methyl.

25

A still further sub-class of compounds according to the invention is represented by the compounds of formula IID, and salts and prodrugs thereof:

T171X



(IID)

17

PS

wherein

P 13  $W^1$  represents nitrogen or C-A<sup>42</sup>;  
n is zero, 1, 2 or 3;  
13 B<sup>4</sup> represents oxygen, sulphur or N-R<sup>43</sup>;  
5 A<sup>41</sup> and A<sup>42</sup> independently represent C<sub>1-6</sub> alkyl,  
C<sub>2-6</sub> alkenyl, C<sub>2-6</sub> alkynyl, C<sub>3-7</sub> cycloalkyl, aryl,  
aryl(C<sub>1-6</sub>)alkyl, C<sub>3-7</sub> heterocycloalkyl, heteroaryl or  
heteroaryl(C<sub>1-6</sub>)alkyl, any of which groups may be  
optionally substituted; or hydrogen, halogen, cyano,  
10 trifluoromethyl, C<sub>1-6</sub> alkoxy, C<sub>1-6</sub> alkylthio or -NR<sup>X</sup>R<sup>Y</sup>;  
P 13 R<sup>41</sup> represents -CH<sub>2</sub>.CHR<sup>44</sup>.NR<sup>46</sup>R<sup>47</sup> or a group of  
formula

— Ti80X



P R<sup>42</sup>, R<sup>43</sup>, R<sup>44</sup>, R<sup>45</sup>, R<sup>46</sup> and R<sup>47</sup> independently  
represent hydrogen or C<sub>1-6</sub> alkyl; and  
P R<sup>X</sup> and R<sup>Y</sup> independently represent hydrogen,  
hydrocarbon or a heterocyclic group, or R<sup>X</sup> and R<sup>Y</sup> together  
25 represent a C<sub>2-6</sub> alkylene group.  
P Examples of optional substituents on the groups  
A<sup>41</sup> and A<sup>42</sup> correspond to those indicated for the groups  
A<sup>11</sup> and A<sup>12</sup> with respect to formula IIA above. Particular  
values of A<sup>41</sup> and A<sup>42</sup> with respect to formula IID include  
30 hydrogen and methyl.

Preferably, R<sup>42</sup>, R<sup>43</sup> and R<sup>44</sup> each represents  
hydrogen. Preferred values of R<sup>45</sup>, R<sup>46</sup> and R<sup>47</sup> include  
hydrogen and methyl.

P Specific compounds within the scope of the present invention include:

PO 2-[5-(2-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

5 PO 2-[5-(1-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

PO N,N-dimethyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

PO N,N-dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

10 PO N,N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

PO N,N-dimethyl-2-[5-(tetrazol-2-ylmethyl)-1H-indol-3-yl]ethylamine;

15 PO N,N-dimethyl-2-[5-(tetrazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

PO N,N-dimethyl-2-[5-(1-methyl-1,2,4-triazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

PO N,N-dimethyl-2-[5-(1-methyl-1,2,4-triazol-3-ylmethyl)-1H-indol-3-yl]ethylamine;

20 PO N,N-dimethyl-2-[5-(1,2,3-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

PO 3-(2-aminoethyl)-5-(1-methyltetrazol-5-yl)benzo[b]thiophene;

25 PO 3-(2-aminoethyl)-5-(2-methyltetrazol-5-yl)benzo[b]thiophene;

PO 3-[2-(N,N-dimethylamino)ethyl]-5-(2-methyltetrazol-5-yl)benzo[b]thiophene;

PO N,N-dimethyl-2-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

30 PO N,N-dimethyl-2-[5-(imidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

PO N,N-dimethyl-2-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]ethylamine;

PO N,N-dimethyl-2-[5-(2-ethyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

PO N,N-dimethyl-2-[5-(1-ethyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine;

5 PO N,N-dimethyl-2-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]ethylamine;

PO 1-methyl-4-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]piperidine;

PO 1-methyl-4-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]piperidine;

10 10 yl]piperidine;

PO 4-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]piperidine;

11 4-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]piperidine;

12 3-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]pyrrolidine;

13 1-methyl-3-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]pyrrolidine;

15 15 yl]pyrrolidine;

PO 4-[5-(imidazol-1-yl)-1H-indol-3-yl]piperidine;

16 4-[5-(1,2,3-triazol-1-yl)-1H-indol-3-yl]piperidine;

17 1-methyl-4-[5-(imidazol-1-yl)-1H-indol-3-yl]piperidine;

18 1-methyl-4-[5-(1,2,3-triazol-1-yl)-1H-indol-3-yl]piperidine;

20 20 yl]piperidine;

PO 1-methyl-3-[5-(1,2,3-triazol-1-yl)-1H-indol-3-yl]pyrrolidine;

PO 1-methyl-3-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]pyrrolidine;

25 25 1-methyl-3-[5-(imidazol-1-yl)-1H-indol-3-yl]pyrrolidine;

1-methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]pyrrolidine;

1-methyl-3-[5-(imidazol-1-ylmethyl)-1H-indol-3-yl]pyrrolidine;

30 30 PO N,N-dimethyl-2-[5-(2-aminoimidazol-1-yl)-1H-indol-3-yl]ethylamine;

PO N,N-dimethyl-2-[5-(2-aminoimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine;

PO 8 9 N-methyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-~~o~~  
y1]ethylamine;

PS and salts and prodrugs thereof.

P The invention also provides pharmaceutical  
5 compositions comprising one or more compounds of this  
invention in association with a pharmaceutically  
acceptable carrier. Preferably these compositions are in  
unit dosage forms such as tablets, pills, capsules,  
powders, granules, sterile parenteral solutions or  
10 suspensions, metered aerosol or liquid sprays, drops,  
ampoules, auto-injector devices or suppositories; for  
oral, parenteral, intranasal, sublingual or rectal  
administration, or for administration by inhalation or  
insufflation. For preparing solid compositions such as  
15 tablets, the principal active ingredient is mixed with a  
pharmaceutical carrier, e.g. conventional tabletting  
ingredients such as corn starch, lactose, sucrose,  
sorbitol, talc, stearic acid, magnesium stearate,  
dicalcium phosphate or gums, and other pharmaceutical  
20 diluents, e.g. water, to form a solid preformulation  
composition containing a homogeneous mixture of a  
compound of the present invention, or a non-toxic  
pharmaceutically acceptable salt thereof. When referring  
25 to these preformulation compositions as homogeneous, it  
is meant that the active ingredient is dispersed evenly  
throughout the composition so that the composition may be  
readily subdivided into equally effective unit dosage  
forms such as tablets, pills and capsules. This solid  
30 preformulation composition is then subdivided into unit  
dosage forms of the type described above containing from  
0.1 to about 500 mg of the active ingredient of the  
present invention. The tablets or pills of the novel  
composition can be coated or otherwise compounded to  
provide a dosage form affording the advantage of

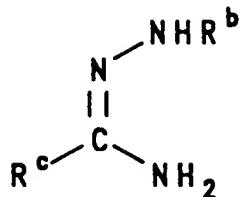
prolonged action. For example, the tablet or pill can comprise an inner dosage and an outer dosage component, the latter being in the form of an envelope over the former. The two components can be separated by an enteric layer which serves to resist disintegration in the stomach and permits the inner component to pass intact into the duodenum or to be delayed in release. A variety of materials can be used for such enteric layers or coatings, such materials including a number of polymeric acids and mixtures of polymeric acids with such materials as shellac, cetyl alcohol and cellulose acetate.

The liquid forms in which the novel compositions of the present invention may be incorporated for administration orally or by injection include aqueous solutions, suitably flavoured syrups, aqueous or oil suspensions, and flavoured emulsions with edible oils such as cottonseed oil, sesame oil, coconut oil or peanut oil, as well as elixirs and similar pharmaceutical vehicles. Suitable dispersing or suspending agents for aqueous suspensions include synthetic and natural gums such as tragacanth, acacia, alginate, dextran, sodium carboxymethylcellulose, methylcellulose, polyvinyl-pyrrolidone or gelatin.

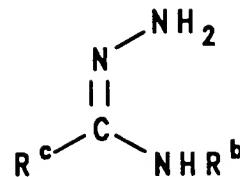
In the treatment of migraine, a suitable dosage level is about 0.01 to 250 mg/kg per day, preferably about 0.05 to 100 mg/kg per day, and especially about 0.05 to 5 mg/kg per day. The compounds may be administered on a regimen of 1 to 4 times per day.

The 1,2,4-triazole compounds of this invention may be prepared by a process which comprises reacting a reactive derivative of a carboxylic acid of formula  $R^a-CO_2H$  with a compound either of formula III or of formula IV, or a salt thereof:

T230X



(III)



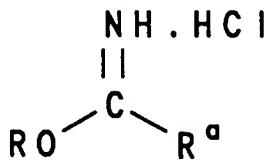
(IV)

PS wherein one of  $\text{R}^a$ ,  $\text{R}^b$  and  $\text{R}^c$  is a group of formula  $\text{A}^1$ ,  
10 another is a group of formula  $\text{A}^2$ , and the third is a  
group of formula  $-\text{E}-\text{F}$ , as defined with reference to  
formula I above.

P Suitable reactive derivatives of the acid  
 $\text{R}^a\text{-CO}_2\text{H}$  include esters, for example  $\text{C}_{1-4}$  alkyl esters;  
15  $^{13}\text{C}$  thioesters, for example pyridylthioesters; acid  
 $^{13}\text{C}$  anhydrides, for example  $(\text{R}^a\text{-CO})_2\text{O}$ ; acid halides, for  
example acid chlorides; orthoesters; and primary,  
secondary and tertiary amides.

P A preferred reactive derivative of the acid  
20  $^{13}\text{C}$   $\text{R}^a\text{-CO}_2\text{H}$  is the iminoether derivative of formula V:

T231X



(V)

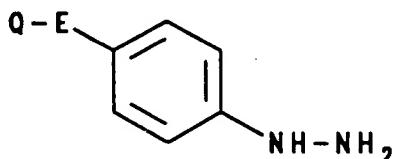
PS where  $\text{R}$  is  $\text{C}_{1-4}$  alkyl.

P The reagent of formula III may be generated in  
30 situ in the reaction mixture. For example, the reaction  
may be effected by treating a compound of formula V above  
with an alkyl hydrazine, e.g. methyl hydrazine, followed  
by a suitable carboxylic acid such as formic acid.

P The reaction is conveniently carried out by heating the reagents together, optionally in a solvent, for example tetrahydrofuran, dimethylformamide or a lower alkanol such as ethanol, propanol or isopropanol, at 5 about 20°C to 100°C for about 1 to 6 hours.

13 Where R<sup>a</sup> is a group of formula -E-F and the group F is an indole moiety of structure FC as defined above, the reactive derivative of a carboxylic acid of 13 formula HO<sub>2</sub>C-E-F may be prepared by reacting a compound 10 of formula VI:

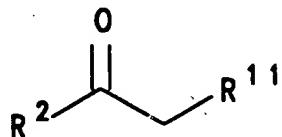
T240X



(VI)

PS wherein Q represents a reactive carboxylate moiety, and E is as defined above; with a compound of formula VII or a 20 carbonyl-protected form thereof:

T241X



(VII)

PS wherein R<sup>2</sup> is as defined above and R<sup>11</sup> corresponds to the group R<sup>1</sup> as defined above or represents a group of 13 formula -CH<sub>2</sub>.CHR<sup>4</sup>D<sup>1</sup>, in which R<sup>4</sup> is as defined above and D<sup>1</sup> 30 represents a readily displaceable group; followed, where required, by N-alkylation by standard methods to introduce the moiety R<sup>3</sup>.

24

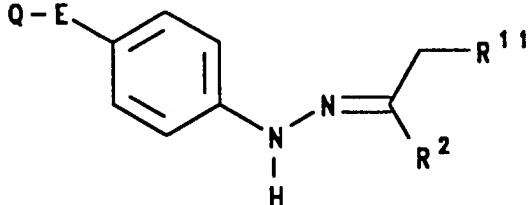
Suitable carbonyl-protected forms of the compounds of formula VII include the dimethyl acetal or ketal derivatives.

The readily displaceable group D<sup>1</sup> in the compounds of formula VII suitably represents a halogen atom, preferably chlorine. When the moiety R<sup>11</sup> in the compounds of formula VII is a group of formula 5 -CH<sub>2</sub>.CHR<sup>4</sup>D<sup>1</sup>, the substituent D<sup>1</sup> is displaced in situ under the prevailing reaction conditions to afford a final 10 product of formula I wherein R<sup>1</sup> represents a group of 13 formula -CH<sub>2</sub>.CHR<sup>4</sup>.NH<sub>2</sub>. The terminal amino group can subsequently, if desired, be further elaborated using techniques known from the art to give a compound of formula I wherein R<sup>1</sup> represents the required group of 15 13 formula -CH<sub>2</sub>.CHR<sup>4</sup>.NR<sup>6</sup>R<sup>7</sup>.

The reaction of compounds VI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula VIII:

20

T250X

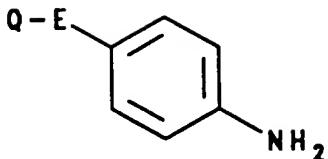


(VIII)

*PS* wherein Q, E, R<sup>2</sup> and R<sup>11</sup> are as defined above; followed by cyclisation using a suitable reagent, such as a 30 13 polyphosphate ester, to give a compound of formula Q-E-F.

*P* The hydrazines of formula VI may be prepared from the corresponding anilines of formula IX:

T260X

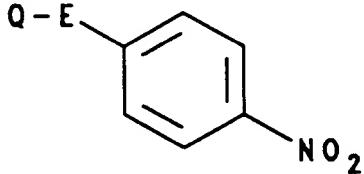


(IX)

*PS* wherein Q and E are as defined above; by diazotisation followed by reduction. Diazotisation is typically 10 carried out using sodium nitrite/conc. HCl and the resulting diazo product reduced *in situ* using, for example, tin(II) chloride/conc. HCl or sodium sulphite/conc. HCl.

*P* The anilines of formula IX may be prepared by 15 reduction of the corresponding nitro compounds of formula X:

T261X



(X)

*PS* wherein Q and E are as defined above; typically by 25 catalytic hydrogenation or using tin(II) chloride.

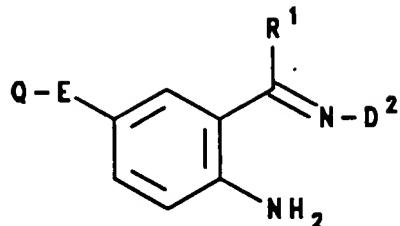
*P* Where they are not commercially available, the nitro compounds of formula X may be synthesized by standard methods well known to those skilled in the art.

13 Where R<sup>a</sup> is a group of formula -E-F and the 30 group F is an indazole moiety of structure FB as defined above, the reactive derivative of a carboxylic acid of

13 formula HO<sub>2</sub>C-E-F may be prepared by the cyclisation of a compound of formula XI:

26

T270X



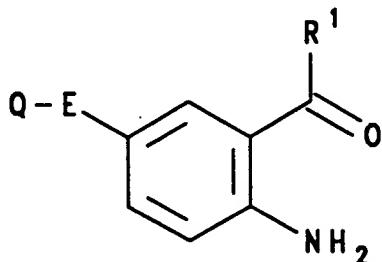
(XI)

PS wherein Q, E and R¹ are as defined above; and D²  
10 represents a readily displaceable group; followed, where  
required, by N-alkylation by standard methods to  
introduce the moiety R³.

P The cyclisation of compound XI is conveniently  
achieved in a suitable organic solvent at an elevated  
15 temperature, for example in a mixture of m-xylene and  
2,6-lutidine at a temperature in the region of 140°C.

The readily displaceable group D² in the  
compounds of formula XI suitably represents a C₁-₄  
alkanoyloxy group, preferably acetoxy. Where D² in the  
20 desired compound of formula XI represents acetoxy, this  
compound may be conveniently prepared by treating a  
carbonyl compound of formula XII:

T271X



(XII)

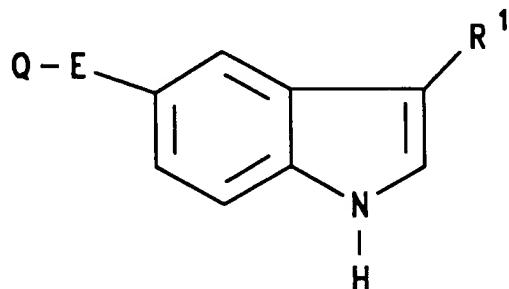
PS wherein R¹, E and Q are as defined above; or a protected  
derivative thereof; with hydroxylamine hydrochloride,  
advantageously in pyridine at the reflux temperature of

the solvent; followed by acetylation with acetic anhydride, advantageously in the presence of a catalytic quantity of 4-dimethylaminopyridine, in dichloromethane at room temperature.

5

P The N-formyl protected derivative of the intermediate of formula XII may be conveniently prepared by ozonolysis of an indole derivative of formula XIII:

T280X



(XIII)

PS

wherein R¹, E and Q are as defined above; followed by a reductive work-up, advantageously using dimethylsulphide.

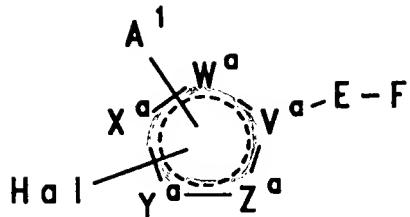
20

P The indole derivative of formula XIII may be prepared by methods analogous to those described in the accompanying Examples, or by procedures well known from the art.

25

In an alternative process, the triazole compounds according to the invention may be prepared by a method which comprises reacting a compound of formula XIV:

T290X



10 PS wherein A¹, E and F are as defined above, Hal represents halogen, and two of V², W², X², Y² and Z², to one of which the group Hal is attached, represent carbon and the remainder represent nitrogen; with a reagent which

31 provides an anion  ${}^{-}A^2$ , where A² is as previously defined.

15 P 31 Reagents which may provide the anion  ${}^{-}A^2$  include Grignard reagents  $A^2MgHal$  (where Hal = halogen); organocuprate reagents such as  $LiA^2Cu$ ; organolithium reagents  $A^2Li$ ; or compounds which stabilise the anion by means of an adjacent activating group such as an ester or 20 enolisable ketone function. In this case, the adjacent ester or ketone function may be retained after the process is complete, or may be removed. For example, an ester moiety may be hydrolysed and decarboxylated.

25 The 1,2,3-triazole compounds according to the present invention may be prepared by a process which comprises the cycloaddition of an alkyne of formula R²-C≡C-R³ with an azide of formula R⁴-N₃, where R², R³ and R⁴ are as defined above.

13, 57 The cycloaddition reaction may be conveniently effected in a suitable solvent such as tetrahydrofuran, 30 ideally by heating in an autoclave for 8 hours.

57, 13 The tetrazole compounds in accordance with the invention may be prepared by a process which comprises the cycloaddition of a nitrile of formula N≡C-R⁴ with an

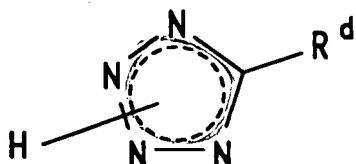
13 azide of formula  $R^e-N_3$ , where one of  $R^d$  and  $R^e$  represents a group of formula  $A^1$  and the other is a group of formula  
13 -E-F, as defined previously.

The cycloaddition reaction is conveniently  
5 effected by heating the reactants together at an elevated  
temperature, e.g. a temperature in the region of  $150^{\circ}\text{C}$ ,  
in a suitable solvent such as N-methylpyrrolid-2-one,  
advantageously in the presence of triethylamine  
hydrochloride. The product obtained from the  
10 cycloaddition reaction will generally be a mixture of  
isomers substituted by the  $A^1$  group at positions 1 and 2  
of the tetrazole ring, corresponding to structures IL and  
IM respectively as defined above. These isomers may  
conveniently be separated using conventional techniques  
15 such as chromatography.

In an alternative process, the tetrazole  
compounds of the invention may be prepared by a method  
which comprises reacting a compound of formula  $R^e-L$  with  
a tetrazole derivative of formula XV:

20

T300X



(XV)

PS wherein one of  $R^d$  and  $R^e$  represents a group of formula  $A^1$   
13 and the other is a group of formula -E-F, as defined  
30 above, and L represents a suitable leaving group; in the  
presence of a base such as triethylamine.

P The leaving group L suitably represents  
halogen, e.g. bromine or iodine, or a sulphonate  
derivative such as tosylate or mesylate.

30

P

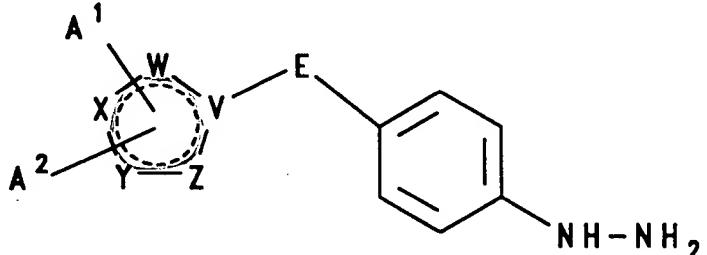
The reaction is conveniently carried out in a suitable organic solvent, e.g. acetonitrile, at room temperature.

5 The tetrazole derivatives of formula XV may be prepared by cycloaddition of a nitrile of formula  $N\equiv C-R^d$  with sodium azide, advantageously under the conditions described above for the reaction between the nitrile  $N\equiv C-R^d$  and the azide  $R^e-N_3$ ; followed by acidification with a mineral acid such as hydrochloric acid.

57, 13

10 In a further process, the compounds according to the invention wherein the group F is an indole moiety of structure FC as defined above may be prepared by a method which comprises reacting a compound of formula XVI:

15  
T310X



(XVI)

PS

wherein V, W, X, Y, Z, A¹, A² and E are as defined above; with a compound of formula VII as defined above, or a carbonyl-protected form thereof, e.g. the dimethyl acetal or ketal; followed, where required, by N-alkylation by standard methods to introduce the moiety R³.

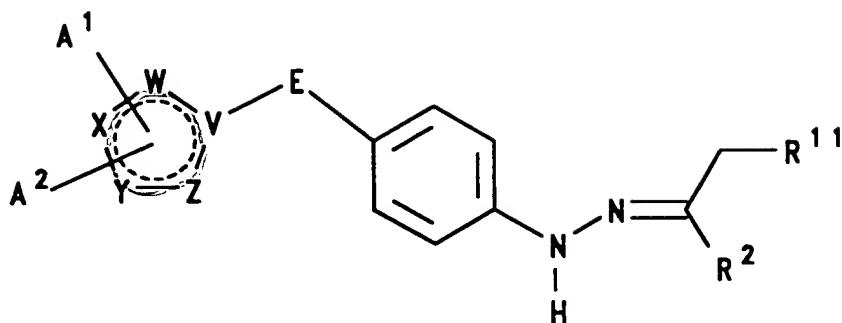
P

As with that between compounds VI and VII, the reaction between compounds XVI and VII may be carried out in a single step (Fischer indole synthesis) or by an initial non-cyclising step at a lower temperature to give a compound of formula XVII:

T320X

- 31 -

T1092Y

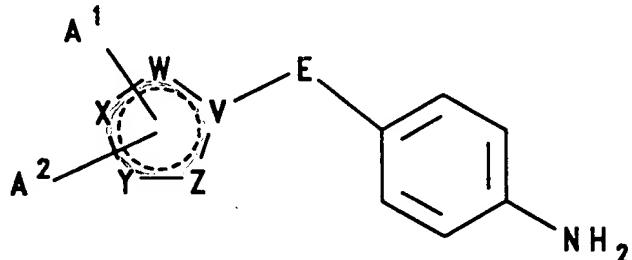


(XVII)

PS wherein V, W, X, Y, Z, A<sup>1</sup>, A<sup>2</sup>, E, R<sup>2</sup> and R<sup>11</sup> are as defined above; followed by cyclisation using a suitable reagent, e.g. a polyphosphate ester.

P The hydrazines of formula XVI may be prepared  
15 from the corresponding anilines of formula XVIII:

T321X

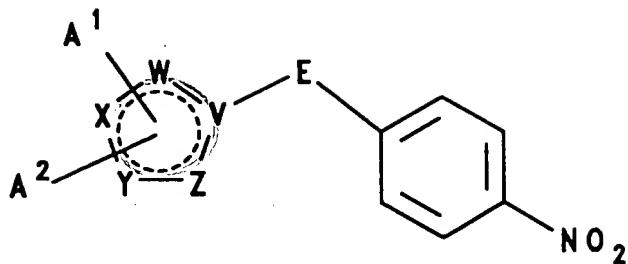


(XVIII)

PS wherein V, W, X, Y, Z, A<sup>1</sup>, A<sup>2</sup> and E are as defined above; 25 by methods analogous to those described above with reference to the compounds of formula IX.

P The anilines of formula XVIII may be prepared from the corresponding nitro compounds of formula XIX:

T330X

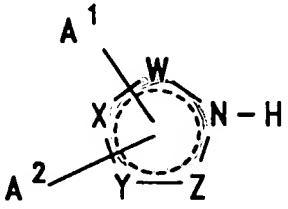


(XIX)

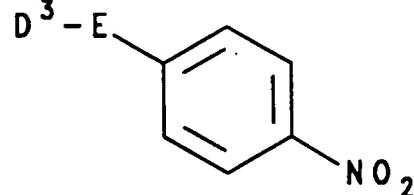
PS wherein V, W, X, Y, Z, A<sup>1</sup>, A<sup>2</sup> and E are as defined above;  
10 by methods analogous to those described above with  
reference to the compounds of formula X.

P The nitro compounds of formula XIX may be  
prepared by a variety of methods which will be readily  
apparent to those skilled in the art. For example, where  
15 V represents a nitrogen atom, the relevant compounds of  
formula XIX may be prepared by reacting the anion of a  
compound of formula XX with a compound of formula XXI:

T331X



(XX)



(XXI)

PS wherein W, X, Y, Z, A<sup>1</sup>, A<sup>2</sup> and E are as defined above, and  
D<sup>3</sup> represents a readily displaceable group.

P Where compound XX is a triazole or tetrazole  
derivative, the anion thereof may be generated by  
30 carrying out the reaction in a base such as  
triethylamine. Where compound XX is an imidazole  
derivative, the anion thereof may conveniently be  
generated if the reaction is carried out in sodium  
hydride using N,N-dimethylformamide as solvent. Where

salts of the compounds of formula XX are commercially available, e.g. the sodium salt of 1,2,4-triazole, these are advantageously utilised in N,N-dimethylformamide solution in place of the compounds of formula XX 5 themselves, with no requirement in this instance for additional base to be present in the reaction mixture.

The readily displaceable group D<sup>3</sup> in the compounds of formula XXI is suitably a halogen atom, preferably bromine; except when the moiety D<sup>3</sup> is attached 10 directly to the aromatic ring, i.e. when E represents a bond, in which case D<sup>3</sup> is preferably fluorine.

Where they are not commercially available, the nitro compounds of formula XXI above may be prepared by procedures analogous to those described in the 15 accompanying Examples, or by methods well known from the art.

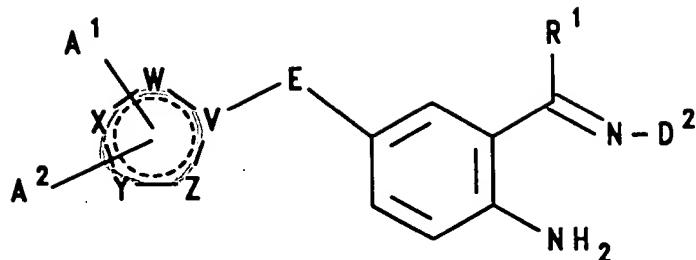
In an alternative approach to the 1,2,4-triazole derivatives, the nitro compounds of formula XIX may be prepared from those of formula X above by 20 appropriate modification of the moiety Q using, for example, methods analogous to those described above with reference to the compounds of formulae III and IV. Thus, for example, since Q in the compounds of formula X represents a reactive carboxylate moiety, the compounds 25 of formula XIX may be prepared therefrom by reaction with a compound of formula A<sup>2</sup>-C(=NNH<sub>2</sub>)NH<sub>2</sub> or A<sup>2</sup>-C(=NNH<sub>2</sub>)NHA<sup>1</sup>.  
13 50

In a still further process, the compounds according to the invention wherein the group F is an indazole moiety of structure FB as defined above may be 30 prepared by a method which comprises cyclising a compound of formula XXII:

T350X

- 34 -

T1092Y



(XXII)

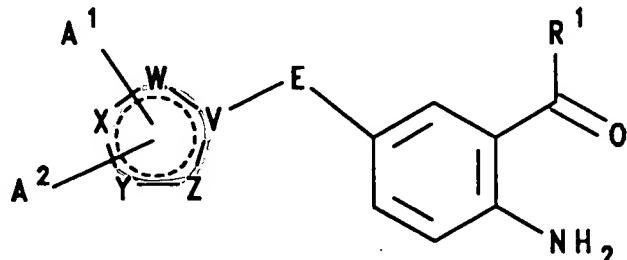
PS wherein V, W, X, Y, Z, A<sup>1</sup>, A<sup>2</sup>, E, R<sup>1</sup> and D<sup>2</sup> are as defined above; followed, where required, by N-alkylation by standard methods to introduce the moiety R<sup>3</sup>.

P As with the cyclisation of compound XI, that of compound XXII is conveniently achieved in a suitable organic solvent at an elevated temperature, for example in a mixture of m-xylene and 2,6-lutidine at a temperature in the region of 140°C.

The compounds of formula XXII may, for example, be prepared from the corresponding compound of formula XXIII:

20

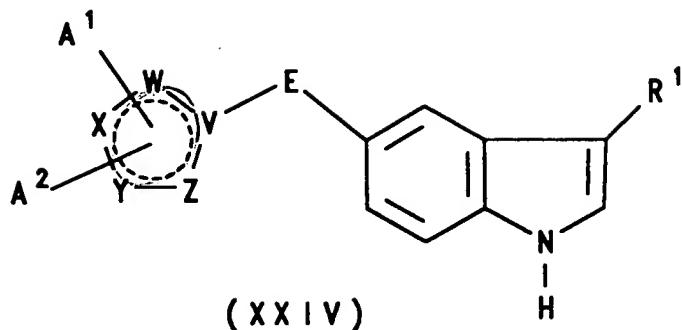
T351X



(XXIII)

PS wherein V, W, X, Y, Z, A<sup>1</sup>, A<sup>2</sup>, E and R<sup>1</sup> are as defined above; or a protected derivative thereof; which in turn 30 may be prepared from the corresponding compound of formula XXIV:

T360X

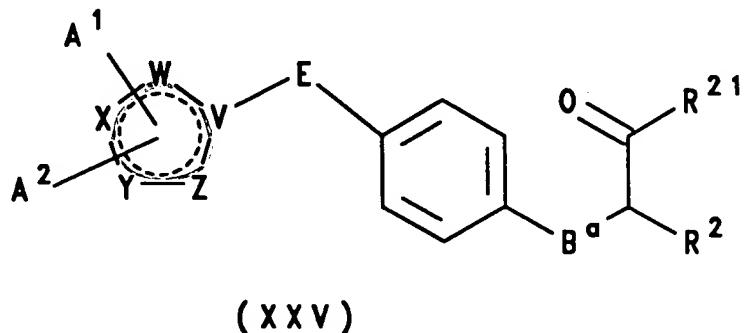


PS wherein V, W, X, Y, Z, A<sup>1</sup>, A<sup>2</sup>, E and R<sup>1</sup> are as defined above; using methods analogous to those described above with reference to the compounds of formulae XII and XIII. Thus, for example, since Q in the compounds of formula XIII represents a reactive carboxylate moiety, the 1,2,4-triazole derivatives of formula XXIV may be prepared therefrom by reaction with a compound of formula

13 50 A<sup>2</sup>-C(=NNHA<sup>1</sup>)NH<sup>2</sup> or A<sup>2</sup>-C(=NNH<sub>2</sub>)NHA<sup>1</sup>.

P In a yet further process, the compounds according to the invention wherein the group F is a benzofuran or benzthiophene moiety may be prepared by a 20 method which comprises cyclising a compound of formula XXV:

T361X



30 PS wherein V, W, X, Y, Z, A<sup>1</sup>, A<sup>2</sup>, E and R<sup>2</sup> are as defined above, B<sup>a</sup> represents oxygen or sulphur, and R<sup>21</sup> corresponds to the group R<sup>1</sup> as defined above or represents a precursor group thereto as discussed below;

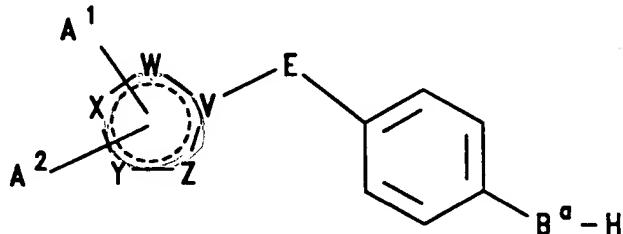
36

followed, where required, by conversion of the group  $R^{21}$  into the desired group  $R^1$  by conventional means.

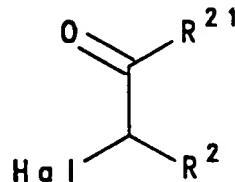
$\rho$  The cyclisation is conveniently effected by using polyphosphoric acid or a polyphosphate ester, 5 advantageously at an elevated temperature.

The compounds of formula XXV may be prepared by reacting a compound of formula XXVI with a compound of formula XXVII:

T370X



(XXVI)



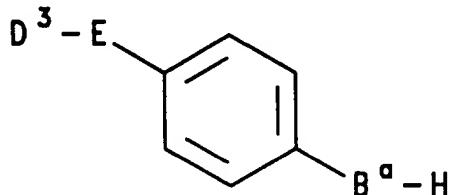
(XXVII)

$\rho$  where in  $V$ ,  $W$ ,  $X$ ,  $Y$ ,  $Z$ ,  $A^1$ ,  $A^2$ ,  $E$ ,  $B^a$ ,  $R^2$  and  $R^{21}$  are as defined above, and Hal represents halogen.

$\rho$  The reaction is conveniently effected in the 20 presence of a base such as sodium hydroxide.

The hydroxy and mercapto derivatives of formula XXVI may be prepared by a variety of methods which will be readily apparent to those skilled in the art. In one such method, the anion of a compound of formula XX as defined above is reacted with a compound of formula 25 XXVIII:

T371X



(XXVIII)

PS wherein D<sup>3</sup>, E and B<sup>a</sup> are as defined above; to afford an intermediate of formula XXVI wherein V is nitrogen.

P The compounds of formula XXVII and XXVIII, where they are not commercially available, may be 5 prepared by standard procedures well known in the art.

It will be understood that any compound of formula I initially obtained from any of the above processes may, where appropriate, subsequently be elaborated into a further compound of formula I by 10 techniques known from the art. Indeed, as will be appreciated, the compound of formula XV above in which R<sup>d</sup> is a group of formula -E-F is itself a compound of formula I in which A<sup>1</sup> is hydrogen and A<sup>2</sup> represents a non-<sup>a</sup> bonded electron pair. In particular, a compound of 15 formula I wherein R<sup>3</sup> is hydrogen initially obtained may be converted into a compound of formula I wherein R<sup>3</sup> represents C<sub>1-6</sub> alkyl, C<sub>2-6</sub> alkenyl or C<sub>2-6</sub> alkynyl by standard techniques such as alkylation, for example by treatment with an alkyl iodide, e.g. methyl iodide, 20 typically under basic conditions, e.g. sodium hydride in dimethylformamide, or triethylamine in acetonitrile.

Similarly, a compound of formula I wherein R<sup>1</sup> represents 13 a group of formula -CH<sub>2</sub>.CHR<sup>4</sup>.NH<sub>2</sub> initially obtained may be converted into a compound of formula I wherein R<sup>1</sup> 25 13 represents a group of formula -CH<sub>2</sub>.CHR<sup>4</sup>.NR<sup>6</sup>R<sup>7</sup> in which R<sup>6</sup> and R<sup>7</sup> are as defined above with the exception of hydrogen, for example by conventional N-alkylation or N-<sup>a</sup> arylation techniques, e.g. by treatment with the appropriate aldehyde in the presence of a reducing agent 30 such as sodium cyanoborohydride.

Where the above-described processes for the preparation of the compounds according to the invention give rise to mixtures of stereoisomers, these isomers may

be separated by conventional techniques such as preparative chromatography.

The novel compounds may be prepared in racemic form, or individual enantiomers may be prepared either by 5 enantiospecific synthesis or by resolution. The novel compounds may, for example, be resolved into their component enantiomers by standard techniques, such as the formation of diastereomeric pairs by salt formation with an optically active acid, such as  $(-)$ -di-p-toluoyl- $d_6$  10 tartaric acid and/or  $(+)$ -di-p-toluoyl- $l$ -tartaric acid followed by fractional crystallization and regeneration of the free base. The novel compounds may also be resolved by formation of diastereomeric esters or amides, followed by chromatographic separation and removal of the 15 chiral auxiliary.

During any of the above synthetic sequences it may be necessary and/or desirable to protect sensitive or reactive groups on any of the molecules concerned. This may be achieved by means of conventional protecting 20 groups, such as those described in Protective Groups in Organic Chemistry, ed. J.F.W. McOmie, Plenum Press, 1973; and T.W. Greene, Protective Groups in Organic Synthesis, John Wiley & Sons, 1981. The protecting groups may be removed at a convenient subsequent stage using methods 25 known from the art.

Alternatively, certain of the functional groups on the desired products may be carried through the reaction sequence as precursor groups, and then regenerated from these precursor groups at a late stage 30 in the overall synthesis. For example, where  $R^1$  in the desired compound of formula I represents a group of 13 formula  $-(CH_2)_2NH_2$ , this group can be generated from a 14 cyano precursor  $-CH_2CN$  by reduction using, for example, borane/tetrahydrofuran. The cyano precursor may in turn

be carried through the reaction sequence as a methyl  
13 group -CH<sub>3</sub>, which may conveniently be converted to -CH<sub>2</sub>CN  
by treatment with N-bromosuccinimide and benzoyl  
peroxide, in the presence of a bright light source,  
5 followed by reaction of the resulting bromo intermediate  
with sodium cyanide in dimethyl sulphoxide.

The following Examples illustrate the  
preparation of compounds according to the invention.

The ability of test compounds to bind to  
10 5-HT<sub>1</sub>-like receptors was measured in membranes prepared  
from pig caudate using the procedure described in  
J. Neurosci., 1987, 7, 894. Binding was determined using  
2 nM 5-hydroxytryptamine creatinine sulphate,  
8, 9 5-[1,2-<sup>3</sup>H(N)] as a radioligand. Cyanopindolol (100 nM)  
15 and mesulergine (100 nM) were included in the assay to  
block out 5-HT<sub>1A</sub> and 5-HT<sub>1C</sub> binding sites respectively.  
The concentration of the compounds of the accompanying  
Examples required to displace 50% of the specific binding  
82 (IC<sub>50</sub>) is below 1 μM in each case.

20 The activity of test compounds as agonists of  
the 5-HT<sub>1</sub>-like receptor was measured in terms of their  
ability to mediate contraction of the saphenous vein of  
New Zealand White rabbits, using the procedure described  
in Arch. Pharm., 1990, 342, 111. Agonist potencies were  
25 calculated as -log<sub>10</sub>EC<sub>50</sub> (pEC<sub>50</sub>) values, from plots of  
82 percentage 5-HT (1 μM) response against the concentration  
of the agonist. The compounds of the accompanying  
Examples were found to possess pEC<sub>50</sub> values in this assay  
of not less than 5.0 in each case.

DE

CL

EXAMPLE 1

CL 8

2-[5-(2-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

5

P

1. 4-Hydrazinobenzylcyanide. Hydrochloride

10

A solution of NaNO<sub>2</sub> (80g, 1.16mol) was added dropwise to a cooled (-10°C), stirred, suspension of 4-aminobenzyl cyanide (153.5g, 1.16mol) in concentrated HCl (1500ml), at such a rate

15

31 that the temperature did not rise above -10°C. The mixture was stirred at -10°C for 0.25h before being filtered rapidly under vacuum into an addition funnel. The solution was added portionwise over a 0.25h period to a rapidly stirred mixture of SnCl<sub>2</sub>.2H<sub>2</sub>O (1.05kg, 4.64mol) in concentrated HCl (800ml) keeping the temperature below -5°C. The mixture was allowed to warm to room temperature and stir for 0.25h before filtering the sandy coloured precipitate under vacuum and washing with ether (5 x 500ml). The resultant solid was dried over P<sub>2</sub>O<sub>5</sub> in a vacuum oven (80°C) for 16h to give the title compound (213g, 100%), m.p. 181-183°C; <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 3.90 (2H, s, CH<sub>2</sub>); 7.06 (2H, d, J = 8.7Hz, Ar-H); 7.40 (2H, d, J = 8.7Hz, Ar-H).

P

2. 2-(5-Cyanomethyl-1H-indol-3-yl)ethylamine.

Hydrochloride

P 4-Chlorobutanal dimethylacetal (37.07g, 0.24mol) was  
5 added to a stirred solution of 4-hydrazinobenzyl cyanide  
hydrochloride (47.0g, 0.26mol) in EtOH/H<sub>2</sub>O (5:1; 21) and  
refluxed for 4.5h. The reaction mixture was evaporated to  
dryness under vacuum, MeOH (150ml) added, and the mixture  
left at 0°C for 10h. The resultant pale yellow precipitate was  
10 33 filtered under vacuum, washed with Et<sub>2</sub>O/MeOH (5:1; 2 x  
100ml) and dried. The product was used without further  
14 purification (24.1g, 40%), m.p. 239-241°C; R<sub>f</sub> 0.4 in  
CH<sub>2</sub>Cl<sub>2</sub>/EtOH/NH<sub>3</sub> (40:8:1); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) 3.18 (2H,  
t, J = 7.1Hz, CH<sub>2</sub>); 3.36 (2H, t, J = 7.1Hz, CH<sub>2</sub>); 4.02 (2H, s,  
15 CH<sub>2</sub>); 7.22 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.36 (1H, s, Ar-H);  
7.56 (1H, d, J = 8.4Hz, Ar-H); 7.66 (1H, s, Ar-H).

P

3. 2-(5-Tetrazol-5-ylmethyl-1H-indol-3-yl)ethylamine

20

A solution of 2-(5-cyanomethyl-1H-indol-3-yl)ethylamine  
hydrochloride (2.5g, 10.6mmol), triethylamine hydrochloride  
(2.2g, 16.0mmol) and sodium azide (2.1g, 32.3mmol), in 15  
methylpyrrolidin-2-one (30ml) was heated at 140°C for 8h. 5N  
hydrochloric acid (3ml) was added and the solvents removed by  
25 distillation under vacuum. The residue was chromatographed  
on silica-gel eluting with EtOH/Et<sub>2</sub>O/H<sub>2</sub>O/NH<sub>3</sub> (20:30:8:1) to  
give the title-tetrazole (1.76g, 69%); δ (360MHz, CD<sub>3</sub>OD) 3.06  
(2H, t, J = 7.2Hz, CH<sub>2</sub>); 3.19 (2H, t, J = 7.2Hz, CH<sub>2</sub>); 4.29 (2H, s,

CH<sub>2</sub>); 7.07 (1H, d, J = 8.4Hz, Ar-H); 7.13 (1H, s, Ar-H); 7.29 (1H, d, J = 8.4Hz, Ar-H); 7.44 (1H, s, Ar-H).

P 4. N-tert-Butyloxycarbonyl-2-(5-tetrazol-5-ylmethyl-1H-indol-3-yl)ethylamine

P To a stirred suspension of 2-(5-tetrazol-5-ylmethyl-1H-indol-3-yl)ethylamine (1.76g, 7.27mmol) in dry CH<sub>2</sub>Cl<sub>2</sub> (40ml) was added triethylamine (1.5g, 14.9mmol) and (BOC)<sub>2</sub>O (1.9g, 7.3mmol) and the mixture stirred for 16h. The solvent was removed under vacuum and the residue chromatographed on silica-gel eluting with EtOH/Et<sub>2</sub>O/H<sub>2</sub>O/NH<sub>3</sub> (20:60:8:1) to give the title product (1.6g, 64%); δ (360MHz, CD<sub>3</sub>OD) 1.41 (9H, s, 3 of CH<sub>3</sub>); 2.87 (2H, t, J = 7.4Hz, CH<sub>2</sub>); 3.30 (2H, t, J = 7.4Hz, CH<sub>2</sub>); 4.32 (2H, s, CH<sub>2</sub>); 6.99 (1H, d, J = 8.3Hz, Ar-H); 7.04 (1H, s, Ar-H); 7.26 (1H, d, J = 8.3Hz, Ar-H); 7.49 (1H, s, Ar-H).

P 8 5. N-tert-Butyloxycarbonyl-2-[5-(2-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine and N-tert-butyloxycarbonyl-2-[5-(1-benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine

P Benzyl bromide (0.31g, 1.8mmol) was added to a solution of the tetrazole from step 4 (0.62g, 1.8mmol), and triethylamine (0.37g, 3.6mmol) in dry acetonitrile (20ml). The mixture was stirred at R.T. for 2h, heated at 70°C for 1h and then stirred at

R.T. for 16h. The solvent was removed under vacuum and the residue chromatographed through silica-gel eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (97:3) to give 2-separated benzyl tetrazoles. The less polar isomer was identified as the 2-benzyl tetrazole (0.17g, 54%)  $\delta$  (360MHz,  $\text{CDCl}_3$ ) 1.43 (9H, s, 3 of  $\text{CH}_3$ ); 2.90 (2H, t,  $J$  = 6.8Hz,  $\text{CH}_2$ ); 3.41 (2H, br t,  $\text{CH}_2$ ); 4.32 (2H, s,  $\text{CH}_2$ ); 5.70 (2H, s,  $\text{CH}_2\text{Ph}$ ); 7.00 (1H, s, Ar-H); 7.15 (1H, d,  $J$  = 8.4Hz, Ar-H); 7.28 (1H, d,  $J$  = 8.4Hz, Ar-H); 7.34 (5H, s, Ar-H); 7.50 (1H, s, Ar-H); 7.96 (1H, br s, NH).

10

P The more polar component was identified as the 1 $\beta$  benzyltetrazole (0.2g, 26.4%)  $\delta$  (360MHz,  $\text{CDCl}_3$ ) 1.43 (9H, s, 3 of  $\text{CH}_3$ ); 2.88 (2H, t,  $J$  = 7.0Hz,  $\text{CH}_2$ ); 3.40 (1H, br t,  $\text{CH}_2$ ); 4.26 (2H, s,  $\text{CH}_2$ ); 5.29 (2H, s,  $\text{CH}_2\text{-Ph}$ ); 6.92 (1H, d,  $J$  = 8.4Hz, Ar-H); 7.01-7.05 (3H, m, Ar-H); 7.27-7.30 (5H, m, Ar-H); 8.08 (1H, br s, NH).

P8

9 yl]ethylamine. Oxalate

20

P Trifluoroacetic acid (1.5ml) was added to a solution of the less polar component isolated from step 5 (0.17g, 0.4mmol) in  $\text{CH}_2\text{Cl}_2$  (5ml) and stirred at R.T. for 1h. The solvents were removed under vacuum and the residue chromatographed through silica-gel eluting with  $\text{CH}_2\text{Cl}_2/\text{EtOH}/\text{NH}_3$  (40:8:1) to give the title-tetrazole. The oxalate salt was prepared (65mg); 14 mp 169-171°C; (Found: C, 59.23; H, 5.07; N, 19.60.

$C_{19}H_{20}N_6 \cdot 1.05 (C_2H_2O_4)$  requires C, 59.36; H, 5.22; N, 19.68%;  $\delta$  (360MHz,  $D_2O$ ) 3.09 (2H, t,  $J$  = 6.9Hz,  $CH_2$ ); 3.29 (2H, t,  $J$  = 6.9Hz,  $CH_2$ ); 4.30 (2H, s,  $CH_2$ ); 5.77 (2H, s,  $CH_2$ ); 7.11 (1H, dd,  $J$  = 1.6 and 8.4Hz, Ar-H); 7.28 (1H, s, Ar-H); 7.32 (1H, s, Ar-H); 7.34 and 7.39-7.41 (5H, m, Ar-H); 7.43 (1H, d,  $J$  = 8.4Hz, Ar-H); 7.51 (1H, s, Ar-H).

Cl

EXAMPLE 2

10 8 2-[5-(1-Benzyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Hydrochloride. Hemihydrate

P Prepared from the more polar component isolated from step 5, Example 1, using the procedure described for step 6, Example 1. The hydrochloride hemihydrate salt was prepared; 14 mp 210-213°C; (Found: C, 60.39; H, 5.88; N, 22.14.  $C_{19}H_{20}N_6 \cdot HCl \cdot 0.5H_2O$  requires C, 60.39; H, 5.87; N, 22.24%);  $\delta$  (250MHz,  $D_2O$ ) 3.02 (2H, t,  $J$  = 6.8Hz,  $CH_2$ ); 3.19 (2H, t,  $J$  = 6.8Hz,  $CH_2$ ); 4.44 (2H, s,  $CH_2$ ); 5.60 (2H, s,  $CH_2$ ); 6.95-7.02 (3H, m, Ar-H); 7.16-7.25 (4H, m, Ar-H); 7.28 (1H, s, Ar-H); 7.40 (1H, d,  $J$  = 8.4Hz, Ar-H).

Cl

EXAMPLE 3

25 8 N,N-Dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

P 8 1. N-tert-Butyloxycarbonyl-2-[5-(2-methyltetrazol-5-

9 ylmethyl)-1H-indol-3-yl]ethylamine and N-tert $\ominus$   
8 butyloxycarbonyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-  
9 yl]ethylamine

5 P Methyl iodide (0.44g, 3.1mmol) was added to a stirred solution of the tetrazole from step 4, Example 1 (0.95g, 2.78mmol) and triethylamine (0.56g, 5.5mmol) in dry acetonitrile (15ml). After 10h a further equivalent of methyl iodide was added and stirred for 16h. The solvent was removed  
10 under vacuum and the residue chromatographed on silica-gel eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}$  (97:3) to give the title mixture of 1 $\ominus$  and 2-methyltetrazoles (0.6g, 61%);  $\delta$  (360MHz,  $\text{CDCl}_3$ ) 1.43  
14 (9H, m, 3 of  $\text{CH}_3$ ); 2.89-2.92 (2H, m,  $\text{CH}_2$ ); 3.38-3.48 (2H, m,  $\text{CH}_2$ ); 3.83 (2H, s,  $\text{CH}_2$ ); 4.28 and 4.40 (total 3H, s,  $\text{CH}_3$ ); 6.98  
15 and 7.17 (total 1H, d,  $J$  = 8.4Hz, Ar-H); 7.02 and 7.06 (total 1H, s, Ar-H); 7.30 and 7.31 (total 1H, d,  $J$  = 8.4Hz, Ar-H); 7.43 and 7.54 (total 1H, s, Ar-H); 8.00 and 8.10 (total 1H, br s, NH).

PG 2. 2-[5-(2-Methyltetrazol-5-ylmethyl)-1H-indol-3-  
20 L<sup>9</sup> yl]ethylamine and 2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-  
L 3-yl]ethylamine

P Prepared from the preceding methyltetrazoles using the procedure described in step 6, Example 1. The crude product  
25 was chromatographed on silica-gel eluting with  $\text{CH}_2\text{Cl}_2/\text{EtOH}/\text{NH}_3$  (40:8:1) to give 2 separated components. The less polar product (0.1g, 24%) was identified as the 2 $\ominus$

47 methyltetrazole;  $\delta$  (360MHz,  $\text{CDCl}_3$ ) 1.38 (9H, s, 3 of  $\text{CH}_3$ ); 2.88 (2H, t,  $J$  = 6.6Hz,  $\text{CH}_2$ ); 3.00 (2H, t,  $J$  = 6.6Hz,  $\text{CH}_2$ ); 4.28 (3H, s,  $\text{CH}_3$ ); 4.33 (2H, s,  $\text{CH}_2$ ); 7.00 (1H, d,  $J$  = 8.4Hz, Ar-H); 7.06 (1H, d,  $J$  = 2.1Hz, Ar-H); 7.17 (1H, d,  $J$  = 8.4Hz, Ar-H); 7.56 (1H, s, Ar-H); 8.04 (1H, br s, NH).

ρ The more polar product (0.13g, 31%) was identified as the  
47 1-methyltetrazole;  $\delta$  (360MHz,  $\text{CDCl}_3$ ) 1.38 (9H, s, 3 of  $\text{CH}_3$ );  
2.86 (2H, t,  $J$  = 6.6Hz,  $\text{CH}_2$ ); 3.00 (2H, t,  $J$  = 6.6Hz,  $\text{CH}_2$ ); 3.82  
10 (3H, s,  $\text{CH}_3$ ); 4.40 (2H, s,  $\text{CH}_2$ ); 6.98 (1H, dd,  $J$  = 1.6 and 8.3Hz,  
Ar-H); 7.06 (1H, d,  $J$  = 1.6Hz, Ar-H); 7.31 (1H, d,  $J$  = 8.3Hz, Ar-  
H); 7.41 (1H, s, Ar-H); 8.18 (1H, br s, NH).

ρ 8 3. N,N-Dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate  
15 9

ρ A solution of formaldehyde (80mg of a 30% solution) in  
8 methanol (15ml) was added to a stirred solution of 2-[5-(2-  
9 methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine (0.1g,  
20 0.4mmol),  $\text{NaCNBH}_3$  (60mg) and glacial acetic acid (0.12g) in  
methanol (15ml). The solution was stirred for 2h, basified with  
K<sub>2</sub>CO<sub>3</sub> solution and the MeOH removed under vacuum. The  
crude product obtained after extraction into ethylacetate and  
removal of solvent was chromatographed through silica-gel  
25 eluting with  $\text{CH}_2\text{Cl}_2/\text{EtOH}/\text{NH}_3$  (40:8:1) to give the desired  
N,N-dimethyltryptamine (96mg, 87%). The oxalate salt was  
14 prepared: mp 185-187°C (MeOH/Et<sub>2</sub>O); (Found: C, 54.42; H,  
N, 7.12)

47

5.74; N, 22.53.  $C_{15}H_{20}N_6 \cdot C_2H_2O_4$  requires C, 54.54; H, 5.92;  
6 N, 22.45%);  $\delta$  (360MHz,  $D_2O$ ) 2.91 (6H, s, 2 of  $CH_3$ ); 3.21 (2H, t,  
J = 7.4Hz,  $CH_2$ ); 3.47 (2H, t, J = 7.4Hz,  $CH_2$ ); 4.30 (3H, s,  $CH_3$ );  
4.34 (2H, s,  $CH_2$ ); 7.17 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.33  
5 (1H, s, Ar-H); 7.48 (1H, d, J = 8.4Hz, Ar-H); 7.59 (1H, s, Ar-H).

Cl

EXAMPLE 4

8 N,N-Dimethyl-2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate  
9

8 Prepared from 2-[5-(1-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine (0.125g, 0.49mmol) using the procedure described in step 3, Example 3. The free base (0.11g, 80%) obtained was converted to the oxalate salt and recrystallised from MeOH/Et<sub>2</sub>O; mp 176-177°C; (Found: C, 54.21; H, 5.84; N, 22.36.  $C_{15}H_{20}N_6 \cdot C_2H_2O_4$  requires C, 54.54; H, 5.92; N, 22.45%);  $\delta$  (360MHz,  $D_2O$ ); 2.91 (6H, s, 2 of  $CH_3$ ); 3.21 (2H, t, J = 7.4Hz,  $CH_2$ ); 3.40 (2H, t, J = 7.4Hz,  $CH_2$ ); 4.00 (3H, s,  $CH_3$ ); 4.43 (2H, s,  $CH_2$ ); 7.13 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.35 (1H, s, Ar-H); 7.50 (1H, d, J = 8.4Hz, Ar-H); 7.54 (1H, s, Ar-H).

Cl

EXAMPLE 5

8 N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate Hemihydrate  
9

P

1. 1-(4-Nitrophenyl)methyl-1,2,4-triazole

4-Nitrobenzylbromide (21.6g, 0.1mol) was added to a rapidly stirred suspension of 1,2,4-triazole sodium salt (9.1g, 0.1mol) in anhydrous DMF (100ml) and the mixture stirred at room temperature for 16h. Ethyl acetate (400ml) was added followed by water (250ml) and the layers separated. The organic phase was washed with water (3 x 250ml), dried ( $MgSO_4$ ) and evaporated. The residue was chromatographed on silica gel eluting with ethyl acetate to give the title-product (10.6g, 52%); m.p. 98-100°C.  $\delta$  (360MHz,  $CDCl_3$ ) 5.47 (2H, s,  $CH_2$ ) 7.40 (2H, d,  $J$  = 9Hz, Ar-H), 8.02 (1H, s, Ar-H), 8.18 (1H, s, Ar-H), 8.23 (2H, d,  $J$  = 9Hz, Ar-H).

15

P

2. 1-(4-Aminophenyl)methyl-1,2,4-triazole. Hydrochloride

20

A solution of 1-(4-nitrophenyl)methyl-1,2,4-triazole (10.0g, 49mmol) in ethanol (50ml), ethyl acetate (50ml), 5N HCl (10ml) and water (10ml) was hydrogenated over 10% Pd/C (1.0g) at 40 p.s.i., in a Parr apparatus, until an uptake of 188 p.s.i., had been observed (approx 10mins). The catalyst was removed by filtration through hyflo and the solvent removed under vacuum.

25

The residue was azeotroped with ethanol (x2) to give the title-amine hydrochloride (10.6g, 100%).  $\delta$  (360MHz,  $D_2O$ ) 5.53 (2H, s,  $CH_2$ ), 7.37-7.48 (4H, m, Ar-H), 8.12 (1H, s, Ar-H), 8.66 (1H, s, Ar-H). 14

P 3. 1-(4-Hydrazinophenyl)methyl-1,2,4-triazole

A solution of sodium nitrite (3.28g, 48mmol) in water (20ml) was added to a solution of the preceding amine hydrochloride (10.0g, 48mmol), in concentrated HCl (40ml), at 5 such a rate that the temperature did not exceed -10°C. After 13 such addition was complete the solution was stirred at 0°C for 0.25h and then added portionwise to a rapidly stirred solution of SnCl<sub>2</sub>.2H<sub>2</sub>O (40g) in concentrated HCl (40ml). The solution was 10 warmed to room temperature and basified with 20% aqueous NaOH solution. The solution was extracted with ethyl acetate 13 (3 x 250ml) and the combined extracts dried (MgSO<sub>4</sub>) and filtered through hyflo. The solution was evaporated to dryness 14 to give the desired hydrazine (5.0g, 56%) m.p. 109-112°C. δ 15 (360MHz, D<sub>6</sub>-DMSO) 3.93 (2H, br s, NH<sub>2</sub>), 5.20 (2H, s, CH<sub>2</sub>), 6.73 (2H, d, J = 8Hz, Ar-H), 7.08 (2H, d, J = 8Hz, Ar-H), 7.92 (1H, s, Ar-H), 8.57 (1H, s, Ar-H).

P 8 Q 4. 2-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine.

P 4-Chlorobutanal dimethylacetal (3.22g, 21.1mmol) was 20 added to a stirred solution of the preceding hydrazine (5.0g, 26.4mmol) in ethanol/water (5:1, 180ml) and 5N HCl (4.5ml) and the solution refluxed for 4h. The solvents were removed 25 under vacuum and the residue chromatographed on silica gel, eluting with CH<sub>2</sub>Cl<sub>2</sub>/EtOH/NH<sub>3</sub> (30:8:1) to give the desired tryptamine (2.4g, 38%). δ(360MHz, CDCl<sub>3</sub>) 2.90 (2H, t, J = 7Hz, 107

CH<sub>2</sub>), 2.99 (2H, t, J = 7Hz, CH<sub>2</sub>), 5.43 (2H, s, CH<sub>2</sub>), 7.10 (1H, s, Ar-H), 7.11 (1H, d, J = 8Hz, Ar-H), 7.39 (1H, d, J = 8Hz, Ar-H), 7.57 (1H, s, Ar-H), 7.94 (1H, s, Ar-H), 8.08 (1H, s, Ar-H).

5 P 8

9 5. N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Oxalate Hemihydrate

P A solution of formaldehyde (37% w/w solution, 0.19g), in methanol (10ml), was added to a mixture of the preceding 10 tryptamine (0.36g, 1.5mmol), NaCNBH<sub>3</sub> (0.225g, 3.6mmol) and glacial acetic acid (0.45g), in methanol (10ml). The mixture was stirred at room temperature for 2h before adding saturated K<sub>2</sub>CO<sub>3</sub> (50ml) and evaporating the methanol. The residue was extracted with ethyl acetate (3 x 100ml) and the combined extracts washed with brine (100ml), dried (K<sub>2</sub>CO<sub>3</sub>), and evaporated. The crude product was chromatographed on silica 15 gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/EtOH/NH<sub>3</sub> (20:8:1) to give the free base of the title-compound (0.21g, 52%). The oxalate 14 hemihydrate salt was prepared, m.p. 165-167°C (MeOH/Et<sub>2</sub>O); 20 (Found: C, 55.53; H, 6.04; N, 18.59. C<sub>15</sub>H<sub>19</sub>N<sub>5</sub>.C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>. $\frac{1}{2}$ 0.55H<sub>2</sub>O requires C, 55.29; H, 6.03; N, 18.96%); m/e 269 (M<sup>+</sup>);  $\delta$  (360MHz, D<sub>2</sub>O) 2.91 (6H, s, NMe<sub>2</sub>), 3.22 (2H, t, J = 7Hz, CH<sub>2</sub>), 3.47 (2H, t, J = 7Hz, CH<sub>2</sub>), 5.52 (2H, s, CH<sub>2</sub>), 7.21 (1H, dd, J = 1.6 and 8.4Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.52 (1H, d, J = 8.4Hz, Ar-H), 7.65 (1H, s, Ar-H), 8.06 (1H, s, Ar-H), 8.56 (1H, s, Ar-H).

cl

EXAMPLE 6

8

N,N-Dimethyl-2-[5-(1,2,3,4-tetrazol-2-ylmethyl)-1H-indol-3-yl]ethylamine Oxalate.

5

P

1. 1-(4-Nitrophenyl)methyl-1,2,3,4-tetrazole and 2-(4-nitrophenyl)methyl-1,2,3,4-tetrazole.

10

P

4-Nitrobenzylbromide (15.42g, 71.3mmol) was added to a stirred solution of 1H-tetrazole (5.0g, 71.3mmol) and triethylamine (7.9g, 78.0mmol) in acetonitrile (100ml). The mixture was stirred at room temperature for 16h, the solvent removed under vacuum and the residue chromatographed on silica gel eluting with dichloromethane to give 2-isomers. The 2-alkylated product was obtained as the less polar product (2.47g,

15

17%);  $\delta$  (360MHz,  $\text{CDCl}_3$ ) 5.92 (2H, s,  $\text{CH}_2$ ), 7.53 (2H, d,  $J = 8.7\text{Hz}$ , Ar-H), 8.25 (2H, d,  $J = 8.7\text{Hz}$ , Ar-H), 8.56 (1H, s, Ar-H).

16

The more polar, major isomer was identified as the 1-alkylation product (11g, 75%);  $\delta$  (360MHz,  $\text{CDCl}_3$ ) 5.73 (2H, s,  $\text{CH}_2$ ), 7.46 (2H, d,  $J = 8.7\text{Hz}$ , Ar-H), 8.27 (2H, d,  $J = 8.7\text{Hz}$ , Ar-H), 8.64 (1H, s, Ar-H).

20

21

22

23

24

25

2-(4-Nitrophenyl)methyl-1,2,3,4-tetrazole (2.47g, 12.1mmol) was hydrogenated as described for Example 5 step 2.

The product (2.55g, 100%) was obtained as the hydrochloride

(~~47~~) salt;  $\delta$  (250MHz,  $D_2O$ ) 5.86 (2H, s,  $CH_2$ ), 7.40 (2H, d,  $J$  = 8.7Hz, Ar-H), 7.36 (2H, d,  $J$  = 8.7Hz, Ar-H), 8.74 (1H, s, Ar-H).

P 8      3. N,N-Dimethyl-2-[5-(1,2,3,4-tetrazol-2-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

P      The preceding amine was converted into the title compound using the general procedures described for Example 5  
14 Steps 3-5. The oxalate salt was prepared and recrystallised  
10 14 from MeOH/Et<sub>2</sub>O; mp 198-199°C; (Found: C, 53.38; H, 5.55; N, 22.63. C<sub>14</sub>H<sub>18</sub>N<sub>6</sub>. C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>. 0.2 (EtOH) requires C, 53.30; H, 5.78; N, 22.74%);  $\delta$ (360MHz,  $D_2O$ ) 2.91 (6H, s, NMe<sub>2</sub>), 3.23 (2H, t,  $J$  = 7.4Hz,  $CH_2$ ), 3.48 (2H, t,  $J$  = 7.4Hz,  $CH_2$ ), 6.01 (2H, s,  $CH_2$ ), 7.30 (1H, dd,  $J$  = 1.6 and 8.4Hz, Ar-H), 7.37 (1H, s, Ar-H), 7.53 (1H, d,  $J$  = 8.4Hz, Ar-H), 7.76 (1H, s, Ar-H), 8.74 (1H, s, Ar-H).

Cl      EXAMPLE 7

20 P 8      N,N-Dimethyl-2-[5-1,2,3,4-tetrazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Succinate

P      1-(4-nitrophenyl)methyl-1,2,3,4-tetrazole was converted into the title-compound using the procedures described for  
25 14 Example 5. The succinate salt was prepared, m.p. 55-56°C (isopropylalcohol); (Found C: 57.08; H, 6.14; N, 23.34. C<sub>14</sub>H<sub>18</sub>N<sub>6</sub>. 0.75 (C<sub>4</sub>H<sub>6</sub>O<sub>4</sub>) requires C, 56.89; H, 6.32; N,

$\delta$  23.42%);  $\delta$  (360MHz,  $D_2O$ ) 2.93 (6H, s,  $NMe_2$ ), 3.23 (2H, t,  $J$  = 7.5Hz,  $CH_2$ ), 3.48 (2H, t,  $J$  = 7.5Hz,  $CH_2$ ), 5.81 (2H, s,  $CH_2$ ), 7.28 (1H, dd,  $J$  = 1.7 and 8.4Hz, Ar-H), 7.39 (1H, s, Ar-H), 7.56 (1H, d,  $J$  = 8.4Hz, Ar-H), 7.75 (1H, s, Ar-H), 9.20 (1H, s, Ar-H).

5

Cl

EXAMPLE 8

8 N,N-Dimethyl-2-[5-(1-methyl-1,2,4-triazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Bisoxalate

10

P 8 9 1. Ethyl 3-[2-(dimethylamino)ethyl]-1H-indole-5-methylcarboximidate. Hydrochloride

P A solution of N,N-dimethyl-2-(5-cyanomethyl-1H-indol-3-yl)ethylamine (5g, 22.01mmol) in ethanol was saturated with HCl gas and the solution stirred at room temperature for 16h. The solvent was removed under vacuum to give the title-product  
4- (6g, 92%);  $\delta$  (360MHz,  $D_6$ -DMSO) 1.29 (3H, t,  $J$  = 7.0Hz,  $CH_2$ ); 2.83 (6H, s,  $NMe_2$ ), 3.13 (2H, t,  $J$  = 7.5Hz,  $CH_2$ ), 3.31 (2H, m,  $CH_2$ ), 4.04 (2H, s,  $CH_2$ ), 4.42 (2H, q,  $J$  = 7.0Hz,  $CH_2$ ), 7.08 (1H, dd,  $J$  = 1.5 and 8.4Hz, Ar-H), 7.27 (1H, s, Ar-H), 7.37 (1H, d,  $J$  = 8.4Hz, Ar-H), 7.48 (1H, br s, NH), 7.71 (1H, s, Ar-H).

P 8 2. N,N-Dimethyl-2-[5-(1-methyl-1,2,4-triazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Bisoxalate  
25 9

8 A mixture of the preceding imide ester (3g, 10.15mmol), methylhydrazine (0.8ml) and triethylamine (3.54ml), in ethanol (30ml), was stirred at room temperature for 3h. The solvent was removed under vacuum and the resultant product dissolved in 5 formic acid (98%, 3.3ml) and the solution stirred for 0.5h at room temperature and refluxed for 2h. The solution was cooled to room temperature, poured into an aqueous solution of  $K_2CO_3$  33 (75ml) and extracted with ethyl acetate (4 x 200ml). The combined extracts were dried ( $MgSO_4$ ) and evaporated, and the 10 residue chromatographed through silica gel eluting with  $CH_2Cl_2/EtOH/NH_3$  (40:8:1) to give 2-components. The less polar isomer was identified as the title-1-methyl-1,2,4-triazole 14 (360mg). The bisoxalate salt was prepared; mp 135-137°C; (Found: C, 50.91; H, 5.38; N, 13.86.  $C_{16}H_{21}N_5$ . 0.25( ethanol) 15  $\delta^+$  requires C, 50.70; H, 5.47; N, 14.08%);  $\delta$  (360MHz,  $D_2O$ ) 2.91 (6H, s,  $NMe_2$ ); 3.23 (2H, t,  $J$  = 7.3Hz,  $CH_2$ ), 3.48 (2H, t,  $J$  = 7.3Hz,  $CH_2$ ), 3.95 (3H, s, Me), 4.48 (2H, s,  $CH_2$ ), 7.13 (1H, dd,  $J$  = 1.5 and 8.4Hz, Ar-H), 7.37 (1H, s, Ar-H), 7.53 (1H, d,  $J$  = 8.4Hz, Ar-H), 7.57 (1H, s, Ar-H), 8.32 (1H, s, Ar-H).

20

Cl

EXAMPLE 9

8 N,N-Dimethyl-2-[5-(1-methyl-1,2,4-triazol-3-ylmethyl)-1H-9-indol-3-yl]ethylamine. Trishydrochloride

25

9 The more polar isomer obtained from Example 8 Step 2

21 was identified as the title-triazole (180mg). The trishydrochloride salt was prepared, mp <40°C (hygroscopic);  
Found: C, 49.80, H, 6.56; N, 16.69.  $C_{16}H_{21}N_5 \cdot 3HCl$ . 0.35  
5  $\delta$  (Et<sub>2</sub>O) requires C, 49.91; H, 6.62; N, 16.73%);  $\delta$  (360MHz, D<sub>2</sub>O)  
2.91 (6H, s, NMe<sub>2</sub>); 3.23 (2H, t, J = 7.4Hz, CH<sub>2</sub>), 3.49 (2H, t, J = 7.4Hz, CH<sub>2</sub>), 3.95 (3H, s, Me), 4.27 (2H, s, CH<sub>2</sub>), 7.17 (1H, dd, J = 1.5 and 8.5Hz, Ar-H), 7.34 (1H, s, Ar-H), 7.50 (1H, d, J = 8.5Hz, Ar-H), 7.60 (1H, s, Ar-H), 8.88 (1H, s, Ar-H).

10 Cl

EXAMPLE 10

8 N,N-Dimethyl-2-[5-(1,2,3-triazol-1-ylmethyl)-1H-indol-3-  
9 yl]ethylamine. Oxalate.

15 P

1. 1-(4-nitrophenyl)methyl-1,2,3-triazole

4-Nitrobenzylbromide (25.4g, 0.12mol) was added to a solution of 1H-1,2,3-triazole (8.12g, 0.12mol) and triethylamine (11.88g, 0.12mol) in anhydrous acetonitrile. The mixture was refluxed for 1h, cooled to room temperature and the precipitated NEt<sub>3</sub>·HBr filtered off. The solvent was removed under vacuum and the residue chromatographed through silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub> (100) to CH<sub>2</sub>Cl<sub>2</sub>/MeOH (95.5) to give 2-products. The more polar product was identified as the title-1-isomer (13g, 14 25  $\delta$  54%); mp 114-116°C  $\delta$  (250MHz, CDCl<sub>3</sub>) 5.72 (2H, s, CH<sub>2</sub>), 7.38 (2H, d, J = 9Hz, Ar-H), 7.64 (1H, s, Ar-H), 7.78 (1H, s, Ar-H), 8.18 (2H, d, J = 9Hz, Ar-H). The less polar, minor isomer was

14 identified as the 2-alkylation product (2.25g, 9%), mp 112-113°C.  
17 δ (250MHz, CDCl<sub>3</sub>) 5.72 (2H, s, CH<sub>2</sub>), 7.40 (2H, d, J = 9Hz, Ar-H), 7.66 (2H, s, Ar-H), 8.18 (2H, d, J = 9Hz, Ar-H).

5 P 8 2. N,N-Dimethyl-2-[5-(1,2,3-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate  
9

P 1-(4-nitrophenyl)methyl-1,2,3-triazole was converted into the title-indole using the general procedures described for 14 example 5. The oxalate salt was prepared mp 210-212°C, (Found: C, 55.88; H, 5.75; N, 18.69. C<sub>15</sub>H<sub>19</sub>N<sub>5</sub>·1.1(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>)  
17 0.15H<sub>2</sub>O requires C, 55.67; H, 5.84; N, 18.87%), δ (360MHz, D<sub>2</sub>O). 2.90 (6H, s, NMe<sub>2</sub>), 3.22 (2H, t, J = 7.4Hz, CH<sub>2</sub>), 3.46 (2H, t, J = 7.4Hz, CH<sub>2</sub>), 5.72 (2H, s, CH<sub>2</sub>), 7.24 (1H, dd, J = 1.6 and 8.4Hz, Ar-H), 7.36 (1H, s, Ar-H), 7.52 (1H, d, J = 8.4Hz, Ar-H), 15 7.66 (1H, s, Ar-H), 7.79 (1H, s, Ar-H), 8.00 (1H, d, J = 1Hz, Ar-H)

C

EXAMPLE 11

20 3 - (2 - Aminoethyl)-5 - (2 - methyl-tetrazol-5-yl)benzo[b]thiophene. Oxalate.

P

Step 1

25

4-Bromophenylmercaptopropanone

P To a stirred solution of 4-bromothiophenol (5.09g, 26.9mmol) in NaOH (1.08g, 26.9mmol) and water (32ml) was added chloroacetone (2.17ml, 27.3mmol) and the mixture was stirred under nitrogen for 45min before extracting with ether, 5 washing with water, drying ( $\text{Na}_2\text{SO}_4$ ) and evaporating *in vacuo*, leaving 6.89g (100%) of the title compound as a white  $\left(\text{CDCl}_3\right)$  solid,  $\delta$  2.27 (3H, s), 3.65 (2H, s), 7.20 (2H, d,  $J$  = 8.5Hz), 7.41 (2H, d,  $J$  = 8.5Hz).

10 P Step 2

8,9 5-Bromo-3-methyl benzo[b]thiophene

To a gently refluxing mixture of polyphosphoric acid 15 (4.47g) and chlorobenzene (100ml) was added 40 bromophenylmercaptopropanone (2.24g, 9.14mmol) portionwise over 1h and the mixture was heated at reflux for 8 days. After cooling the organic phase was decanted off and the residue was 18 33 decomposed with  $\text{H}_2\text{O}$  (~100ml), extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 20 75ml), dried ( $\text{MgSO}_4$ ) and combined with the decanted organic phase. This was evaporated *in vacuo* to leave 2.096g of brown um 1 oil. Distillation on a Kugelröhhr apparatus yielded 1.83g (88%) of 14 the title compound as a pale yellow liquid, bp 100- 110°C/0.35mbar.  $\delta$  ( $\text{CDCl}_3$ ) 2.41 (3H, s), 7.10 (1H, s), 7.43 (1H, 25 dd,  $J$  = 8.5 and 1.9Hz), 7.69 (1H, d,  $J$  = 8.5Hz), 7.64 (1H, d,  $J$  = 1.9Hz).

P

Step 3

8, 9 5-Cyano-3-methyl benzo[b]thiophene

5 To copper (I) cyanide (0.569g, 6.35mmol) was added 50  
8, 9 bromo-3-methyl benzo[b]thiophene (1.179g, 5.19mmol) in N<sub>2</sub>  
14 methylpyrrolidinone (10ml) and the mixture was stirred at 180-  
190°C for 17h. This was then partitioned between ether (75ml)  
and ammonia solution (75ml). The ether layer was separated,  
10 33 washed with more ammonia solution (2 x 50ml), dried (Na<sub>2</sub>  
SO<sub>4</sub>) and evaporated *in vacuo* to leave 0.81g of an off-white  
solid. Chromatography on flash silica, eluting with 10% ethyl  
acetate/petroleum ether yielded 0.76g (85%) of the title  
16 compound as a white solid. δ (CDCl<sub>3</sub>) 2.47 (3H, s), 7.23 (1H, s),  
15 7.55 (1H, dd, J = 8.3 and 1.5Hz), 7.93 (1H, d, J = 8.4Hz), 8.03  
(1H, d, J = 1.4Hz).

P

Step 4

20 8, 9 3-Methyl-5-(tetrazol-5-yl)-benzo[b]thiophene

8, 9 To a solution of 5-cyano-3-methyl benzo[b]thiophene  
(0.194g, 1.12mmol) in N-methylpyrrolidinone (5ml) under  
nitrogen was added triethylamine hydrochloride (0.231g,  
25 1.68mmol) followed by sodium azide (0.234g, 3.59mmol) and the  
33 mixture was extracted with ether (4 x 50ml). The combined  
ether extracts were dried (Mg SO<sub>4</sub>) and evaporated *in vacuo* to

leave 0.78g of a white solid. This was chromatographed on flash silica, eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  (aq) (40:8:1 to 30:8:1), to give 0.246g (100%) of the title product as a white solid.  $\delta$  (DMSO) 2.46 (3H, s), 7.41 (1H, s), 7.98 (1H, d,  $J$  = 8.4Hz), 8.03 (1H, dd,  $J$  = 8.4 and 1.5Hz), 8.36 (1H, d,  $J$  = 0.9Hz).  $m/z$  (Cl<sup>-</sup>,  $\text{NH}_3$ ) 215 (M-H)<sup>+</sup>, 160.

P      Step 5

10      8,9    3-Methyl-5-(2-methyltetrazol-5-yl)benzo[b]thiophene and  
8,9    3-Methyl-5-(1-methyltetrazol-5-yl) benzo[b]thiophene

P      To a mixture of 3-Methyl-5-(tetrazol-5-yl)  
8,9    benzo[b]thiophene (0.241g, 1.12mmol) in acetonitrile (5ml) was  
15      added triethylamine (0.28ml, 2.01mmol), then iodomethane  
(0.486ml, 7.81mmol) followed by DMF (3ml) until a clear  
solution formed. The solution was stirred overnight under  
nitrogen before evaporating *in vacuo* and partitioning the  
residue between water (50ml) and ether (25ml). The aqueous  
20      33 layer was separated and extracted with more ether (2 x 25ml),  
the combined ether extracts were dried ( $\text{Mg SO}_4$ ) and  
evaporated *in vacuo* to leave 0.241g of yellow solid.  
14      Chromatography on flash silica, eluting with 25-40% ethyl  
acetate/petroleum ether gave 0.168g (65%) of the 2-isomer of the  
25      title product as a white solid and 0.063g (24%) of the 1-isomer of  
the title product as a white solid. 2-isomer  $\delta$  ( $\text{CDCl}_3$ ) 2.52 (3H,  
s), 4.42 (3H, s), 7.14 (1H, s), 7.94 (1H, d,  $J$  = 8.4Hz), 8.10 (1H, dd,

LO

*J* = 8.4 and 1.5Hz), 8.51 (1H, s). *m/z* (Cl<sup>+</sup>,NH<sub>3</sub>) 231 (M+H)<sup>+</sup> 1  
47 isomer  $\delta$  (CDCl<sub>3</sub>) 2.50 (3H, s), 4.22 (3H, s), 4.22 (3H, s), 7.23  
(1H, s), 7.64 (1H, dd, *J* = 8.3 and 1.5Hz), 8.03 (1H, d, *J* = 8.4Hz),  
8.12 (1H, d, *J* = 1.6Hz). *m/z* (Cl<sup>+</sup>,NH<sub>3</sub>) 231 (M+H)<sup>+</sup>, 202, 172.

5

P

Step 6

8, 9 3-Cyanomethyl-5-(2-methyltetrazol-5-yl) benzo[b]thiophene

10 To a refluxing mixture of 3-methyl-5-(2-methyltetrazol-5-  
8, 9 yl) benzo[b]thiophene (0.162g, 0.703mmol) and benzoyl peroxide  
(10.6mg) in carbon tetrachloride (10ml) irradiated with two desk  
33 lamps (2 x 60W) was added N-bromosuccinimide (0.126g,  
0.707mmol) in small portions. After the addition was complete  
15 the mixture was heated at reflux for a further 90 min, then  
filtered and the filtrate was evaporated *in vacuo* to leave an  
oil/solid mixture. Chromatography on flash silica, eluting with  
dichloromethane gave 0.161g of crude 3-bromomethyl-5-(2-  
8, 9 methyltetrazol-5-yl) benzo[b]thiophene as a colourless oil.

20

The crude 3-bromomethyl-5-(2-methyl-tetrazol-5-yl)  
8, 9 benzo[b]thiophene (0.145g) in DMSO (0.3ml) was added to a  
mixture of sodium cyanide (29.9mg, 0.61mmol) in DMSO (0.2ml)

47

and the mixture was stirred at 100°C for 2h. After cooling, the mixture was poured into water (10ml) and a brown solid was filtered off, washed with water and dried in a vacuum pistol to leave 73.5mg. The filtrate was extracted with dichloromethane 533 (3 x 30ml) and the combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated *in vacuo* to leave 44.7mg. This was combined with the original solid and chromatographed on flash silica, eluting 14 with 20-50% ethyl acetate/petroleum ether to yield 61.5mg 17 (38%) of the title product as a white solid.  $\delta$  ( $\text{CDCl}_3$ ) 3.99 (2H, s), 4.43 (3H, s), 7.59 (1H, s), 8.00 (1H, d,  $J$  = 8.5Hz), 8.19 (1H, dd,  $J$  = 8.5 and 1.5Hz), 8.47 (1H, s).

P

Step 7

15 L

3-(2-Aminoethyl)-5-(2-methyl-tetrazol-5-yl)

8, 9 benzo[b]thiophene. Oxalate.

20

To a solution of 3-cyanomethyl-5-(2-methyl-tetrazol-5-yl) benzo[b]thiophene (0.434g, 1.70mmol) in THF (16ml) under nitrogen was added dropwise 1.0M borane-tetrahydrofuran complex in THF (5.10ml, 5.10mmol) and the mixture was heated at reflux for 6h. After cooling in an ice-bath the mixture was quenched with 2N HCl (22ml) and heated to reflux for 1h. The THF was then removed *in vacuo* and the residue basified with 25 50% sodium hydroxide solution (4ml) before extracting with 33 dichloromethane (3 x 75ml). The combined extracts were dried ( $\text{K}_2\text{CO}_3$ ) and evaporated *in vacuo* to leave 0.45g.

62

Chromatography on flash silica eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub>(aq) (60:8:1) gave 0.383g (87%) of the title product as a white solid. The oxalate salt was prepared using oxalic acid in methanol/ether to give the title product oxalate as  
5 14 a white solid, m.p. 204-209°C. Analysis found: C, 47.75; H, 4.28;  
47 14 N, 19.28%. Calcd for C<sub>12</sub>H<sub>13</sub>N<sub>5</sub>S. 1.1 C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>: C, 47.59; H,  
4.28; N, 19.54%. δ (DMSO) 3.17-3.21 (4H, m), 4.46 (3H, s), 7.72  
(1H, s), 8.06 (1H, dd, J = 8.4 and 1.4Hz), 8.52(1H, s) m/z  
(CI<sup>+</sup>,NH<sub>3</sub>) 260 (M+H)<sup>+</sup>, 230.

10

① L

EXAMPLE 12

3-(2-Aminoethyl)-5-(1-methyltetrazol-5-yl)

8, 9 benzo[b]thiophene. Oxalate.

15

P

Step 1

8, 9 3-Cyanomethyl-5-(1-methyltetrazol-5-yl) benzo[b]thiophene

20

Following the procedure of Example 11, Step 6, 0.666g (2.89mmol) 3-methyl-5-(1-methyltetrazol-5-yl) benzo[b]thiophene was reacted with 0.515g (2.89mmol) of N<sub>2</sub>O bromosuccinimide and 38.1mg of benzoyl peroxide in 30ml of carbon-tetrachloride. The reaction mixture was evaporated in  
25 14 *vacuo* and chromatographed on flash silica, eluting with 0-3% methanol/dichloromethane to give 0.532g of crude 3-bromo-5-(1-

8, 9 methyltetrazol-5-yl) benzo[b]thiophene.

The crude 3-bromo-5-(1-methyltetrazol-5-yl) 8, 9 benzo[b]thiophene (0.504g) was reacted with 97.7mg (1.99mmol) 5 of sodium cyanide in 1.5ml of DMSO at 100°C for 2h. After cooling, the reaction mixture was poured into water (25ml) and 133 extracted with dichloromethane (6 x 50ml). The combined extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated *in vacuo* to leave 14 0.37g. Chromatography on flash silica, eluting with 30-60% 10 ethyl acetate/petroleum ether yielded 28.0mg (4%) of the title 47 product.  $\delta$  ( $\text{CDCl}_3$ ) 4.00 (2H, s), 4.23 (3H, s), 7.63 (1H, s), 7.73 (1H, dd), 8.08 (1H, d), 8.15 (1H, d).

P  
15      Step 2  
1      3-(2-Aminoethyl)-5-(1-methyltetrazol-5-yl)  
8, 9 benzo[b]thiophene. Oxalate.

P      Following the procedure of Example 11, Step 7, 26.1mg 20 (0.102mmol) of 3-cyanomethyl-5-(1-methyltetrazol-5-yl) 8, 9 benzo[b]thiophene in 2ml of THF was reacted with 0.36ml (0.36mmol) of 1.0M borane-tetrahydrofuran complex in THF. Chromatography on flash silica, eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3(\text{aq})$  (60:8:1) gave 17.7mg (67%) of the title 25 product as a colourless oil. The oxalate salt was prepared using oxalic acid in methanol/ether to give the title product oxalate as 14 a white solid, m.p. 206-212°C. Analysis found: C, 47.55; H, 4.05;

47 14 N, 19.65%. Calcd for  $C_{12}H_{13}N_5S \cdot 1.1C_2H_2O_4$ : C, 47.59; H, 4.28; N, 19.54%.  $\delta$  ( $D_2O$ ) 3.32-3.35 (2H, m), 3.40-3.44 (2H, m), 4.22 (3H, s), 7.64 (1H, s), 7.73 (1H, d,  $J$  = 8.4Hz), 8.19 (1H, s), 8.22 (1H, d, 8.5Hz).

5

Cl

EXAMPLE 13

8 9 3-[2-(N,N-Dimethylamino)ethyl]-5-(2-methyltetrazol-5-yl)  
8 9 benzo[b]thiophene. Oxalate.

10

P To a mixture of -(2-aminoethyl)-5-(2-methyltetrazol-5-yl)  
8,9 benzo[b]thiophene (0.372g, 1.43mmol) and sodium  
cyanoborohydride (0.136g, 2.15mmol) in methanol (3ml) and  
acetic acid (0.247ml, 4.30mmol) cooled in an ice bath was added  
15 38% w/v formaldehyde solution (0.453ml, 5.74mmol) in  
methanol (3ml) dropwise over 5min and the mixture was stirred  
at room temperature for 3h. After this time, saturated  
potassium carbonate solution (30ml) was added and the mixture  
33 was extracted with ethyl acetate (3 x 50ml). The combined  
20 extracts were evaporated *in vacuo* to leave 0.53g.  
Chromatography on flash silica, eluting with 10-30%  
methanol/dichloromethane, gave 0.335g (81%) of the title  
product as a colourless oil. The oxalate salt was prepared using  
oxalic acid in methanol/ether to give the title product oxalate as  
25 14 a white solid, m.p. 214-218°C. Analysis found: C, 50.58; H, 4.80;  
N, 18.28%. Calcd for  $C_{14}H_{17}N_5S \cdot C_2H_2O_4$ : C, 50.92; H, 5.07;  
47 14 N, 18.56%.  $\delta$  (DMSO) 2.84 (6H, s), 3.30-3.42 (4H, m), 4.46 (3H,  
s), 7.69 (1H, s), 8.06 (1H, dd,  $J$  = 8.4 and 1.4Hz), 8.20 (1H, d,  $J$  =

8.4Hz), 8.56 (1H, s).  $m/z$  (Cl<sup>+</sup>,NH<sub>3</sub>) 288 (M+H)<sup>+</sup>.

Cl

EXAMPLE 14

5 8

N,N-Dimethyl-2-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Trisoxalate

9

indol-3-yl]ethylamine Trisoxalate

10

1. 1-(4-Nitrophenyl)methyl-2-methylimidazole

15

33

20 47

6

Sodium hydride (2.45g; 61.0mmol, 60% dispersion in oil) was added to a solution of 2-methylimidazole (5.0g, 60.9mmol) in DMF (100ml). The mixture was stirred at room temperature for 0.25h before adding 4-nitrobenzyl bromide (13.2g, 61.0mmol) and heating at 110°C for 2h followed by stirring at room temperature for 16h. Water (200ml) and ethyl acetate (500ml) were added, the aqueous separated and extracted with ethyl acetate (2 x 500ml). The combined extracts were washed with water (3 x 250ml), dried (MgSO<sub>4</sub>) and evaporated. The crude product was chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (4%) to give the title-product (1.58g, 10.5%); δ (360MHz, CDCl<sub>3</sub>) 2.34 (3H, s, Me); 5.16 (2H, s, CH<sub>2</sub>); 6.67 (1H, d, J = 1.3Hz, Ar-H); 7.03 (1H, d, J = 1.3Hz, Ar-H); 7.19 (2H, d, J = 9.5Hz, Ar-H); 8.22 (2H, d, J = 9.5Hz, Ar-H).

P8

2. N,N-Dimethyl-2-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine Trisoxalate

P      Prepared from the preceding 4-nitrobenzyl imidazole using  
5      the general procedure described for Example 5. The trisoxalate  
14      salt was prepared, mp 160-163°C (MeOH/Et<sub>2</sub>O); (Found: C,  
50.57; H, 5.25; N, 10.60. C<sub>17</sub>H<sub>22</sub>N<sub>4</sub>·2.8(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C,  
47 50.79; H, 5.21; N, 10.48%); m/e 282 (M<sup>+</sup>); δ (360MHz, D<sub>2</sub>O) 2.65  
(3H, s, Me); 2.92 (6H, s, NMe<sub>2</sub>); 3.25 (2H, t, J = 7.3Hz, CH<sub>2</sub>);  
10      3.50 (2H, t, J = 7.3Hz, CH<sub>2</sub>); 5.42 (2H, s, CH<sub>2</sub>); 7.18 (1H, d, J =  
14      8.4Hz, Ar-H); 7.31-7.40 (2H, m, Ar-H); 7.40 (1H, s, Ar-H); 7.56  
(1H, d, J = 8.4Hz, Ar-H); 7.66 (1H, s, Ar-H).

Cl

EXAMPLE 15

15

8      N,N-Dimethyl-2-[5-imidazol-1-ylmethyl-1H-indol-3-yl]ethylamine Bisoxalate

20

P      Prepared from imidazole and 4-nitrobenzyl bromide using  
the procedure described for Example 5. The bisoxalate salt was  
14      prepared, 165-166°C (MeOH/Et<sub>2</sub>O); (Found: C, 53.30; H, 5.34;  
N, 12.18. C<sub>16</sub>H<sub>20</sub>N<sub>4</sub>·2.05(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 53.30; H, 5.36;  
47 N, 12.37%); δ (360MHz, D<sub>2</sub>O) 2.92 (6H, s, NMe<sub>2</sub>); 3.24 (2H, t, J  
= 7.7Hz, CH<sub>2</sub>); 3.48 (2H, t, J = 7.7Hz, CH<sub>2</sub>); 5.50 (2H, s, CH<sub>2</sub>);  
25      7.27 (1H, dd, J = 1.5 and 8.4Hz, Ar-H); 7.37 (1H, s, Ar-H); 7.45  
(1H, s, Ar-H); 7.49 (1H, s, Ar-H); 7.56 (1H, d, J = 8.4Hz, Ar-H);  
7.75 (1H, s, Ar-H); 8.78 (1H, s, Ar-H).

47

cl

EXAMPLE 16

8

N,N-Dimethyl-2-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]ethylamine Sesquioxalate

5 9

P

1. 1-(4-Nitrophenyl)-2-methylimidazole

10      Sodium hydride (4.87g, 122.0mmol, 60% dispersion in oil) was added to a solution of 2-methylimidazole (10g, 122.0mmol) in DMF (100ml) and stirred at room temperature for 0.25h. 10 Fluoro-4-nitrobenzene (17.18g, 122.0mmol) was added to the reaction mixture and stirred at room temperature for 16h. Water (150ml) and ethyl acetate (250ml) were added, the 15 33 aqueous separated and extracted with ethyl acetate (3 x 150ml). The combined extracts were washed with water (3 x 150ml), dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated to give the desired product 17 (11.5g, 47%);  $\delta$  (360MHz,  $\text{CDCl}_3$ ) 2.24 (3H, s, Me); 7.06 (1H, d,  $J$  = 1.5Hz, Ar-H); 7.10 (1H, d,  $J$  = 1.5Hz, Ar-H); 7.50 (2H, d,  $J$  = 20 9.5Hz, Ar-H); 8.38 (2H, d,  $J$  = 9.5Hz, Ar-H).

P 8

9

2. N,N-Dimethyl-2-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]ethylamine Sesquioxalate

25 P

Prepared from the preceding 4-nitrophenyl imidazole using the procedure described for Example 5. The sesquioxalate salt 14 was prepared, mp 185-186°C (iPA/MeOH); (Found: C, 56.17; H, 5.99; N, 13.46.  $\text{C}_{16}\text{H}_{20}\text{N}_4\cdot 1.55\text{C}_2\text{H}_2\text{O}_4$ ). 0.1 EtOH requires C,

68

67 56.19; H, 5.79; N, 13.58%);  $\delta$  (360MHz, D<sub>2</sub>O) 2.55 (3H, s, Me);  
2.93 (6H, s, NMe<sub>2</sub>); 3.26 (2H, t, J = 7.4Hz, CH<sub>2</sub>); 3.51 (2H, t, J =  
7.4Hz, CH<sub>2</sub>); 7.30 (1H, dd, J = 2.0 and 8.7Hz, Ar-H); 7.48 (1H, d,  
J = 2.1Hz, Ar-H); 7.51-7.53 (2H, m, Ar-H); 7.70 (1H, d, J =  
8.7Hz, Ar-H); 7.79 (1H, d, J = 2.0Hz, Ar-H).

ol

EXAMPLE 17

8 N,N-Dimethyl-2-[5-(1,2,4-triazol-1ylmethyl)-1H-indol-3-yl]ethylamine. Succinate. Procedure B

ρ A solution of 1-(4-hydrazinophenyl)methyl-1,2,4-triazole dihydrochloride (2g, 7.6mmol, Example 5 step 3) and 4-N,N-dimethylaminobutanal dimethylacetal (1.8g, 11.2mmol) in 4% aqueous sulphuric acid (70ml) was heated at reflux for 2h. After the reaction mixture was cooled to room temperature, ethyl acetate (200ml) was added and the aqueous basified with K<sub>2</sub>CO<sub>3</sub>. The aqueous was separated and extracted further with ethyl acetate (2 x 150ml). The combined organics were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated, and the residue chromatographed on silica gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/EtOH/NH<sub>3</sub> (30:8:1) to give the title-triazole (610mg, 30%). The succinate salt was prepared by addition of a solution of succinic acid (0.27g, 2.3mmol) in methanol (3ml) to a solution of the triazole (0.61g, 2.3mmol) in methanol (5ml). The solvent was removed under vacuum and the resultant product recrystallised from isopropylalcohol, mp

14 118-120°C; (Found: C, 58.76; H, 6.27; N, 17.79.

$C_{15}H_{19}N_3.C_4H_6O_4$  requires C, 58.90; H, 6.50; N, 18.08%).

cl

EXAMPLE 18

5

8

N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Benzoate

9 yl]ethylamine. Benzoate

P 8 The benzoate salt of N,N-dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine was prepared by addition of a solution of benzoic acid in diethyl ether to a solution of the free base in ethanol/diethyl ether (1:4). The precipitated salt was recrystallised from ethanol, mp 178-180°C; (Found: C, 67.28; H, 6.55; N, 17.66.  $C_{15}H_{19}N_3.C_6H_5CO_2H$  requires C, 67.50; H, 6.44; N, 17.89%);  $^1H$  NMR (360MHz,  $D_2O$ )  $\delta$  2.92 (6H, s,  $NMe_2$ ); 3.22 (2H, t,  $J$  = 7.3Hz,  $CH_2$ ); 3.46 (2H, t,  $J$  = 7.3Hz,  $CH_2$ ); 5.52 (2H, s,  $CH_2$ ); 7.22 (1H, dd,  $J$  = 1.6 and 8.4Hz, Ar-H); 7.36 (1H, s, Ar-H); 7.44-7.58 (4H, m, Ar-H); 7.65 (1H, s, Ar-H); 7.87-7.91 (2H, m, Ar-H); 8.06 (1H, s, Ar-H); 8.54 (1H, s, Ar-H).

20

cl

EXAMPLE 19

8

N,N-Dimethyl-2-[5-(2-ethyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

9 yl]ethylamine. Oxalate

25

P Prepared as described for Example 3, using ethyl iodide.

14 The oxalate salt was prepared, mp 140-142°C; (Found: C, 55.71;

70

H, 6.26; N, 21.35.  $C_{16}H_{22}N_6C_2H_2O_4$  requires C, 55.66; H, 6.23; N, 21.64%);  $^1H$  NMR (360MHz,  $D_2O$ )  $\delta$  1.54 (3H, t,  $J$  = 7.4Hz,  $CH_3$ ); 2.91 (6H, s,  $NMe_2$ ); 3.21 (2H, t,  $J$  = 7.4Hz,  $CH_2$ ); 3.47 (2H, t,  $J$  = 7.4Hz,  $CH_2$ ); 4.34 (2H, s,  $CH_2$ ); 4.64 (2H, q,  $J$  = 7.4Hz,  $CH_2CH_3$ ); 7.17 (1H, dd,  $J$  = 1.5 and 8.4Hz, Ar-H); 7.33 (1H, s, Ar-H); 7.48 (1H, d,  $J$  = 8.4Hz, Ar-H); 7.59 (1H, s, Ar-H).

Cl

EXAMPLE 20

10

8

N,N-Dimethyl-2-[5-(1-ethyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate

9

yl]ethylamine. Oxalate

15

P

Prepared using the procedure described for Example 4, using ethyl iodide. The oxalate salt was prepared, mp 179°C ( $MeOH/Et_2O$ ); (Found: C, 55.59; H, 6.23; N, 21.49.

20

$\omega\bar{\gamma}$

$C_{16}H_{22}N_6C_2H_2O_4$  requires C, 55.66; H, 6.23; N, 21.64%);  $^1H$  NMR (360MHz,  $D_2O$ )  $\delta$  1.32 (3H, t,  $J$  = 7.4Hz,  $CH_3$ ); 2.90 (6H, s,  $NMe_2$ ); 3.21 (2H, t,  $J$  = 7.4Hz,  $CH_2$ ); 3.46 (2H, t,  $J$  = 7.4Hz,  $CH_2$ ); 4.38 (2H, q,  $J$  = 7.4Hz,  $CH_2$ ); 4.47 (2H, s,  $CH_2$ ); 7.14 (1H, dd,  $J$  = 1.5 and 8.4Hz, Ar-H); 7.35 (1H, s, Ar-H); 7.50 (1H, d,  $J$  = 8.4Hz, Ar-H); 7.53 (1H, s, Ar-H).

Cl

EXAMPLE 21

25

8

N,N-Dimethyl-2-[5-(1,2,4-triazol-1-yl)-1H-indol-3-yl]ethylamine. Bisoxalate

9

71

P Prepared as described for Example 16 from 1,2,4-triazole sodium derivative and 1-fluoro-4-nitrobenzene. The bisoxalate salt was prepared, mp 210°C (MeOH/Et<sub>2</sub>O); (Found: C, 50.11; H, 4.78; N, 16.35. C<sub>14</sub>H<sub>17</sub>N<sub>5</sub>. 1.9 (C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 50.14; H, 4.92; N, 16.43%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 2.92 (6H, s, NMe<sub>2</sub>); 3.25 (2H, t, J = 7.4Hz, CH<sub>2</sub>); 3.50 (2H, t, J = 7.4Hz, CH<sub>2</sub>); 7.44 (1H, s, Ar-H); 7.47 (1H, dd, J = 2.0 and 8.7Hz, Ar-H); 7.63 (1H, d, J = 8.7Hz, Ar-H); 7.88 (1H, d, J = 2.0Hz, Ar-H); 8.36 (1H, s, Ar-H); 9.05 (1H, s, Ar-H).

10

Cl

EXAMPLE 22

8 9 4-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-N-  
methylpiperidine. Bisoxalate sesquihydrate

15

P A solution of N-methyl-4-(formylmethyl)piperidine (0.25g, 1.8mmol) and 4-(2-methylimidazolyl)phenyl hydrazine hydrochloride (0.48g, 2.1mmol) in 4% H<sub>2</sub>SO<sub>4</sub> (25ml) was heated at reflux for 16h. The mixture was cooled to room temperature, 20 33 basified with K<sub>2</sub>CO<sub>3</sub> solution and extracted with CH<sub>2</sub>Cl<sub>2</sub> (3 x 75ml). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and evaporated and the residue purified by chromatography on silica-gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/EtOH/NH<sub>3</sub> (60:8:1) to give the title-compound (0.12g). The bisoxalate sesquihydrate salt was 25 14 prepared, mp 65-70°C (hygroscopic); (Found: C, 52.97; H, 5.51; N, 11.07. C<sub>18</sub>H<sub>22</sub>N<sub>4</sub>.2(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).1.5H<sub>2</sub>O requires C, 52.69; H, 5.83; N, 11.17%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 1.96-2.08 (2H, m, CH<sub>2</sub>); 2.31-2.40 (2H, m, CH<sub>2</sub>); 2.56 (3H, s, CH<sub>3</sub>); 2.95 (3H, s,

72

14  $\text{CH}_3$ ); 3.20-3.27 (3H, m, CH and  $\text{CH}_2$ ); 3.64-3.68 (2H, m,  $\text{CH}_2$ );  
7.28 (1H, dd,  $J = 2$  and 8.7Hz, Ar-H); 7.44 (1H, s, Ar-H); 7.48  
(1H, d,  $J = 2$ Hz, Ar-H); 7.53 (1H, d,  $J = 2$ Hz, Ar-H); 7.69 (1H, d,  $J$   
= 8.7Hz, Ar-H); 7.81 (1H, d,  $J = 2$ Hz, Ar-H).

5

Cl

EXAMPLE 23

8 9 4-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]-N-  
methylpiperidine. Oxalate

10

ρ A solution of N-methyl-4-(formylmethyl)piperidine (0.1g,  
0.71mmol) and 4-(1,2,4-triazolylmethyl)phenyl hydrazine  
dihydrochloride (0.185g, 0.71mmol) in 4%  $\text{H}_2\text{SO}_4$  was heated at  
reflux for 2h. The mixture was cooled to room temperature,

15 33 basified with  $\text{K}_2\text{CO}_3$  solution and extracted with  $\text{CH}_2\text{Cl}_2$  (2 x  
100ml). The crude product was chromatographed on silica-gel  
eluting with  $\text{CH}_2\text{Cl}_2/\text{EtOH}/\text{NH}_3$  (40:8:1) to give the title ②

14 compound (60mg). The oxalate salt was prepared, mp 218-  
220°C; (Found: C, 58.61; H, 6.03; N, 17.94.  $\text{C}_{17}\text{H}_{21}\text{N}_5 \cdot 1.02$

20  $(\text{C}_2\text{H}_2\text{O}_4)$  requires C, 58.96; H, 6.38; N, 17.56%);  $^1\text{H}$  NMR

14 (360MHz,  $\text{D}_2\text{O}$ )  $\delta$  1.88-2.02 (2H, m,  $\text{CH}_2$ ); 2.20-2.34 (2H, m,  
1  $\text{CH}_2$ ); 2.92 (3H, s,  $\text{CH}_3$ ); 3.10-3.24 (3H, m, CH and  $\text{CH}_2$ ); 3.60-  
3.64 (2H, m,  $\text{CH}_2$ ); 5.51 (2H, s,  $\text{CH}_2$ ); 7.21 (1H, dd,  $J = 1.5$  and  
8.4Hz, Ar-H); 7.26 (1H, s, Ar-H); 7.51 (1H, d,  $J = 8.4$ Hz, Ar-H);  
25 7.69 (1H, s, Ar-H); 8.05 (1H, s, Ar-H); 8.55 (1H, s, Ar-H).

Cl

EXAMPLE 24

8 9 1H-4-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-piperidine.

Bisoxalate dihydrate

5

P8 9 1. 4-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-N<sub>2</sub>C<sub>6</sub>H<sub>5</sub>benzylpiperidine

P

Prepared from N-benzyl-4-(formylmethyl)piperidine using  
the procedure described for Example 22; <sup>1</sup>H NMR (360MHz,  
CDCl<sub>3</sub>) δ 1.80-1.94 (2H, m, CH<sub>2</sub>); 1.98-2.06 (2H, m, CH<sub>2</sub>); 2.14-  
2.24 (2H, m, CH<sub>2</sub>); 2.33 (3H, s, CH<sub>3</sub>); 2.76-2.85 (1H, m, CH);  
3.02-3.08 (2H, m, CH<sub>2</sub>); 3.60 (2H, s, CH<sub>2</sub>); 7.03-7.10 (4H, m, Ar-H);  
7.26-7.38 (5H, m, Ar-H); 7.41 (1H, d, J = 8.5Hz, Ar-H); 7.52  
(1H, d, J = 1.8Hz, Ar-H); 8.30 (1H, br s, NH).

P8 9 2. 1H-4-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-piperidine. Bisoxalate dihydrate

20 P

To a solution of ammonium formate (0.32g, 5.07mmol) and  
8 9 4-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]-N-benzylpiperidine  
(0.4g, 1.08mmol), in methanol (40ml) was added Pd/C (10%;  
0.4g) and the mixture stirred at 60°C for 3h. The catalyst was  
removed by filtration through celite and the solvent removed  
under vacuum. The residue was taken up into H<sub>2</sub>O (30ml),  
25 basified with NH<sub>3</sub> solution and extracted with ethyl acetate (3 x  
100ml). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and

evaporated and the residue chromatographed through silica-gel eluting with  $\text{CH}_2\text{Cl}_2/\text{MeOH}/\text{NH}_3$  (30:8:1) to give the desired piperidine (0.2g). The bisoxalate dihydrate salt was prepared, mp 80°C (hygroscopic); (Found: C, 50.53; H, 5.54; N, 10.87.

5  $\text{C}_{17}\text{H}_{20}\text{N}_4 \cdot 2(\text{C}_2\text{H}_2\text{O}_4) \cdot 2.2\text{H}_2\text{O}$  requires C, 50.43; H, 5.72; N, 11.20%);  $^1\text{H}$  NMR (360MHz,  $\text{D}_2\text{O}$ )  $\delta$  1.91-2.03 (2H, m,  $\text{CH}_2$ ); 2.30-2.34 (2H, m,  $\text{CH}_2$ ); 2.55 (3H, s,  $\text{CH}_3$ ); 3.19-3.36 (3H, m, CH and  $\text{CH}_2$ ); 3.55-3.62 (2H, m,  $\text{CH}_2$ ); 7.28 (1H, dd,  $J$  = 1.2 and 8.6Hz, Ar-H); 7.44 (1H, s, Ar-H); 7.47 (1H, d,  $J$  = 2.0Hz, Ar-H); 10 7.52 (1H, d,  $J$  = 2.0Hz, Ar-H); 7.69 (1H, d,  $J$  = 8.6Hz, Ar-H); 7.82 (1H, d,  $J$  = 1.2Hz, Ar-H).

Cl

EXAMPLE 25

15 8 9 1H-4-[5-(1,2,4-Triazol-1-ylmethyl)-1H-indol-3-yl]piperidine. Oxalate

16 P Prepared from N-benzyl-4-(formylmethyl)piperidine and 4-(1,2,4-triazolylmethyl)phenyl hydrazine dihydrochloride using the procedures described for Examples 23 and 24. The oxalate salt was prepared, mp 272°C; (Found: C, 58.27; H, 5.56; N, 18.79.  $\text{C}_{16}\text{H}_{19}\text{N}_5 \cdot \text{C}_2\text{H}_2\text{O}_4$  requires C, 58.21; H, 5.70; N, 18.86%);  $^1\text{H}$  NMR (360MHz,  $\text{D}_2\text{O}$ )  $\delta$  1.86-1.98 (2H, m,  $\text{CH}_2$ ); 2.24-2.28 (2H, m,  $\text{CH}_2$ ); 3.15-3.36 (3H, m, CH and  $\text{CH}_2$ ); 3.52-25 3.56 (2H, m,  $\text{CH}_2$ ); 5.51 (2H, s,  $\text{CH}_2$ ); 7.21 (1H, dd,  $J$  = 1.6 and 8.5Hz, Ar-H); 7.27 (1H, s, Ar-H); 7.52 (1H, d,  $J$  = 8.5Hz, Ar-H); 7.70 (1H, d,  $J$  = 1.6Hz, Ar-H); 8.09 (1H, s, Ar-H); 8.60 (1H, s, Ar-H).

cl

EXAMPLE 26

8 9

1H-3-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-pyrrolidine.

Bisoxalate

5

P 8 9 1. 3-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-N-<sup>14</sup>C  
benzylpyrrolidine

P

Prepared from N-benzyl-3- (formylmethyl)pyrrolidine and 4-(2-methylimidazolyl)phenyl hydrazine hydrochloride as described for Example 22; <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 1.98-2.06 (1H, m, CH of CH<sub>2</sub>); 2.34 (3H, s, CH<sub>3</sub>); 2.34-2.44 (2H, m, 2 of CH of CH<sub>2</sub>); 2.71 (1H, t, J = 7.4 Hz, CH of CH<sub>2</sub>); 2.80 (1H, t, J = 6.9Hz, CH of CH<sub>2</sub>); 3.05 (1H, t, J = 8.7Hz, CH of CH<sub>2</sub>) 3.61-3.73 (1H, m, CH); 3.72 (2H, ABq, J = 13Hz, CH<sub>2</sub>); 6.95-7.14 (4H, m, Ar-H); 7.22-7.41 (5H, m, Ar-H); 7.40 (1H, d, J = 8.5Hz, Ar-H); 7.66 (1H, s, Ar-H); 8.30 (1H, br s NH).

P 8 9

2. 1H-3-[5-(2-Methylimidazol-1-yl)-1H-indol-3-yl]-<sup>14</sup>C  
pyrrolidine. Bisoxalate

P

Prepared from the preceding N-benzylpyrrolidine using the procedure described for Example 24. The bisoxalate salt was prepared, mp 210-213°C (methanol/ether); (Found: C, 53.93; H, 5.22; N, 12.50. C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>.2(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 53.81; H, 4.97; N, 12.55%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 2.91-2.30 (1H, m, CH of CH<sub>2</sub>); 2.55 (3H, s, CH<sub>3</sub>); 2.55-2.60 (1H, m, CH of CH<sub>2</sub>); 3.35-3.64 (3H, m, CH and CH<sub>2</sub>); 3.80-3.90 (2H, m, CH<sub>2</sub>); 7.30

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(1H, dd,  $J = 2$  and 8.6Hz, Ar-H); 7.47 (1H, d,  $J = 2$ Hz, Ar-H); 7.50 (1H, s, Ar-H); (7.53 (1H, d,  $J = 2$ Hz, Ar-H); 7.70 (1H, d,  $J = 8.6$ Hz, Ar-H); 7.80 (1H, d,  $J = 2$ Hz, Ar-H).

5 Cl

EXAMPLE 27

8 9 N-Methyl-3-[5-(2-methylimidazol-1-yl)-1H-indol-3-yl]C<sub>2</sub>O  
pyrrolidine. Bisoxalate

10 P 8 To a cooled (0°C), stirred mixture of 1H-3-[5-(2-  
9 methylimidazol-1-yl)-1H-indol-3-yl]pyrrolidine (0.12g,  
0.45mmol), acetic acid (0.136g, 2.3mmol) and NaCNBH<sub>3</sub> (71mg,  
1.1mmol), in methanol (15ml), was added dropwise a solution of  
15 formaldehyde (89mg of a 38% w/w solution in H<sub>2</sub>O, 1.1mmol) in  
methanol (10ml). The mixture was stirred at 0°C for 0.1h before  
warming to room temperature and stirring for 1.5h. Saturated  
K<sub>2</sub>CO<sub>3</sub> solution (10ml) was added and the solvent removed  
under vacuum. The residue was extracted with ethyl acetate (3  
33 x 100ml) and the combined extracts dried (Na<sub>2</sub>SO<sub>4</sub>) and  
20 evaporated. The crude product was chromatographed on silica-  
gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH/NH<sub>3</sub> (60:8:1) to give the title  
14 product (0.1g). The bisoxalate salt was prepared, mp 191-194°C  
(MeOH/Et<sub>2</sub>O); (Found: C, 54.39; H, 5.30; N, 11.87.  
C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>.2(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).0.2H<sub>2</sub>O requires C, 54.36; H, 5.30; N,  
25 14 12.07%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 2.26-2.45 (1H, m, CH of  
CH<sub>2</sub>); 2.55 (3H, s, Me); 2.62-2.75 (1H, m, CH of CH<sub>2</sub>); 3.02 and  
3.03 (total 3H, s, Me); 3.23-3.45 (2H, m, CH<sub>2</sub>); 3.60-3.68, 3.77-

77

14 4.1 and 4.12-4.15 (total 3H, each m, CH and CH<sub>2</sub>); 7.30 (1H, d, J = 8.9Hz, Ar-H); 7.48 (1H, d, J = 2.2Hz, Ar-H); 7.52 (1H, s, Ar-H); 7.53 (1H, d, J = 2.2Hz, Ar-H); 7.70 (1H, d, J = 8.9Hz, Ar-H); 7.78 (1H, s, Ar-H).

5

Cl

EXAMPLE 28

8, 9 1H-4-[5-Imidazol-1-yl-1H-indol-3-yl]piperidine. Bisoxalate

10 P Prepared from N-benzyl-4-(formylmethyl)piperidine and 4-<sup>14</sup>(imidazolyl)phenyl hydrazine hydrochloride using the procedures described for Examples 22 and 24. The bisoxalate

14 salt was prepared, mp 155-157°C; (Found: C, 54.32; H, 5.50; N, 11.66. C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>.2(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).0.3(Et<sub>2</sub>O) requires C, 54.33; H, 5.38; N, 11.96%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 1.90-2.04 (2H, m, CH<sub>2</sub>); 2.32 (2H, br d, J = 13Hz, CH<sub>2</sub>); 3.20-3.32 (3H, m, CH and CH<sub>2</sub>); 3.55-3.60 (2H, m, CH<sub>2</sub>); 7.41-7.44 (2H, m, Ar-H); 7.64 (1H, s, Ar-H); 7.68 (1H, d, J = 8.7Hz, Ar-H); 7.85 (1H, s, Ar-H); 7.92 (1H, d, J = 2Hz, Ar-H); 9.06 (1H, s, Ar-H).

20

Cl

EXAMPLE 29

8, 9 1H-4-[5-(1,2,3-Triazol-1-yl)-1H-indol-3-yl]piperidine. Hemioxalate

25

P Prepared from N-benzyl-4-(formylmethyl)piperidine and 4-

(1,2,3-triazolyl)phenyl hydrazine hydrochloride using the procedures described for Examples 22 and 24. The hemioxalate salt was prepared, mp 278°C (MeOH/Et<sub>2</sub>O); (Found: C, 61.84; H, 6.10; N, 22.21. C<sub>15</sub>H<sub>17</sub>N<sub>5</sub>·0.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 61.53; H, 5.81; N, 22.42%); <sup>1</sup>H NMR (360MHz, D<sub>6</sub>-DMSO) δ 1.66-1.82 (2H, m, CH<sub>2</sub>); 1.98-2.06 (2H, m, CH<sub>2</sub>); 2.83-2.89 (2H, m, CH<sub>2</sub>); 2.98-3.08 (1H, m, CH); 3.21 (2H, br d, J = 12.5Hz, CH<sub>2</sub>); 7.28 (1H, s, Ar-H); 7.51-7.56 (2H, m, Ar-H); 7.93 (1H, s, Ar-H); 8.05 (1H, s, Ar-H); 8.73 (1H, s, Ar-H).

10

CL

EXAMPLE 30

15 <sup>8,9</sup> N-Methyl-4-[5-imidazol-1-yl-1H-indol-3-yl]piperidine.

Sesquioxalate

15

P Prepared from N-methyl-4-(formylmethyl)piperidine and 4<sup>10</sup> (imidazolyl)phenyl hydrazine hydrochloride as described for Example 22. The sesquioxalate salt was prepared, mp 217°C; (Found: C, 57.41; H, 5.83; N, 13.30. C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>·1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>)·0.14(CH<sub>3</sub>OH) requires C, 57.61; H, 5.66; N, 13.34%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 1.94-2.06 (2H, m, CH<sub>2</sub>); 2.34-2.38 (2H, m, CH<sub>2</sub>); 2.94 (3H, s, CH<sub>3</sub>); 3.20-3.27 (3H, m, CH and CH<sub>2</sub>); 3.63-3.67 (2H, m, CH<sub>2</sub>); 7.40-7.43 (2H, m, Ar-H); 7.64 (1H, s, Ar-H); 7.68 (1H, d, J = 8.7Hz, Ar-H); 7.84 (1H, s, Ar-H); 7.90 (1H, d, J = 1.3Hz, Ar-H); 9.07 (1H, s, Ar-H).

cl

EXAMPLE 31

8, 9 N-Methyl-4-[5-(1,2,3-triazol-1-yl)-1H-indol-3-yl]piperidine.

Hemioxalate

5

P Prepared from N-methyl-4-(formylmethyl)piperidine and 4(1,2,3-triazolyl)phenyl hydrazine hydrochloride as described for  
14 Example 22. The hemioxalate salt was prepared, mp 251-254°C  
(MeOH/Et<sub>2</sub>O); (Found: C, 62.21; H, 6.49; N, 21.21.

10 C<sub>16</sub>H<sub>19</sub>N<sub>5</sub>·0.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>)·0.1H<sub>2</sub>O requires C, 62.22; H, 6.20; N,

14 21.34%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 1.69-2.01 (2H, m, CH<sub>2</sub>);  
1.25-2.31 (2H, m, CH<sub>2</sub>); 2.94 (3H, s, CH<sub>3</sub>); 3.04-3.20 (3H, m, CH  
and CH<sub>2</sub>); 3.61-3.65 (2H, m, CH<sub>2</sub>); 7.32 (1H, s, Ar-H); 7.44 (1H,  
dd, J = 1.9 and 8.7Hz, Ar-H); 7.58 (1H, d, J = 8.7Hz, Ar-H); 7.86  
15 (1H, d, J = 1.8Hz, Ar-H); 7.94 (1H, s, Ar-H); 8.29 (1H, s, Ar-H).

cl

EXAMPLE 32

8, 9 N-Methyl-3-[5-(1,2,3-triazol-1-yl)-1H-indol-3-yl]pyrrolidine.

20 Oxalate

P Prepared from N-benzyl-3-(formylmethyl)pyrrolidine and  
4-(1,2,3-triazolyl)phenyl hydrazine hydrochloride as described  
for Examples 26 and 27. The oxalate salt was prepared, mp  
14 154-156°C (MeOH/Et<sub>2</sub>O); (Found: C, 57.06; H, 5.39; N, 19.43.

25 C<sub>15</sub>H<sub>17</sub>N<sub>5</sub>·C<sub>2</sub>H<sub>2</sub>O<sub>4</sub> requires C, 57.14; H, 5.36; N, 19.60%); <sup>1</sup>H  
14 NMR (360MHz, D<sub>2</sub>O) δ 2.23-2.38 (1H, m, CH of CH<sub>2</sub>); 2.55-2.69

14 (1H, m, CH of CH<sub>2</sub>); 3.01 (3H, s, Me); 3.13-3.42 and 3.55-3.60  
(total 2H, each m, CH<sub>2</sub>); 3.70-4.09 (3H, m, CH and CH<sub>2</sub>); 7.39  
(1H, d, J = 8.7Hz, Ar-H); 7.42-7.46 (1H, m, Ar-H); 7.58 (1H, d, J  
= 8.7Hz, Ar-H); 7.62 (1H, s, Ar-H); 7.93 (1H, s, Ar-H); 8.30 (1H,  
5 s, Ar-H).

Cl

EXAMPLE 33

8 N-Methyl-3-[5-(2-methylimidazol-1-ylmethyl)-1H-indol-3-yl]pyrrolidine. Bisoxalate  
10 9

Prepared from N-benzyl-3-(formylmethyl)pyrrolidine and  
4-(2-(methyl)imidazol-1-ylmethyl)phenyl hydrazine  
hydrochloride as described for Examples 26 and 27. The  
15 14 bisoxalate salt was prepared, mp 152-153°C; (Found: C, 55.41;  
H, 5.51; N, 11.61. C<sub>18</sub>H<sub>22</sub>N<sub>4</sub>.2(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 55.69; H,  
14 14 5.52; N, 11.81%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 2.22-2.46 (1H, m,  
CH of CH<sub>2</sub>); 2.58-2.76 (1H, m, CH of CH<sub>2</sub>); 2.65 (3H, s, Me); 3.02  
and 3.03 (total 3H, s, Me); 3.21-3.44, 3.60-3.67, 3.75-3.95 and  
20 4.09-4.14 (total 5H, each m, CH and 2 of CH<sub>2</sub>); 5.42 (2H, s,  
CH<sub>2</sub>); 7.17-7.19 (1H, m, Ar-H); 7.32 (2H, s, Ar-H); 7.39 (1H, d, J  
= 8.4Hz, Ar-H); 7.56 (1H, d, J = 8.4Hz, Ar-H); 7.67 (1H, s, Ar-H).

Cl

EXAMPLE 34

25

8 9 N-Methyl-3-[5-imidazol-1-yl-1H-indol-3-yl]pyrrolidine.  
Bisoxalate

P Prepared from N-benzyl-3-(formylmethyl)pyrrolidine and 4-(imidazolyl)phenyl hydrazine hydrochloride using the procedures described for Examples 26 and 27. The bisoxalate salt was prepared, mp 173-175°C (MeOH/Et<sub>2</sub>O); (Found: C, 53.94; H, 5.07; N, 12.51. C<sub>16</sub>H<sub>18</sub>N<sub>4</sub>.2(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 53.81; H, 4.97; N, 12.55%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 2.26-2.45 and 2.60-2.78 (each 1H, each m, CH<sub>2</sub>), 3.02 and 3.03 (total 3H, each s, Me), 3.23-3.45, 3.61-3.66, 3.78-3.95 and 4.11-4.16 (total 5H, each m, 2 of CH<sub>2</sub> and CH), 7.42 and 7.45 (total 1H, each s, Ar-H), 7.49 (1H, d, J = 9.2Hz, Ar-H), 7.65 (1H, s, Ar-H), 7.69 (1H, d, J = 9.2Hz, Ar-H), 7.86-7.89 (2H, m, Ar-H), 9.09 (1H, s, Ar-H).

Cl

EXAMPLE 35

15

8 N-Methyl-3-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-  
9 yl]pyrrolidine. Sesquioxalate. Hemihydrate

P Prepared from N-benzyl-3-(formylmethyl)pyrrolidine and 4-(1,2,4-triazolylmethyl)phenyl hydrazine dihydrochloride as described for Examples 26 and 27. The sesquioxalate hemihydrate salt was prepared, mp 59-61°C (isopropyl alcohol/Et<sub>2</sub>O); (Found: C, 55.10; H, 5.79; N, 16.99. C<sub>16</sub>H<sub>19</sub>N<sub>5</sub>.1.3(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).0.4H<sub>2</sub>O requires C, 55.08; H, 5.57; N, 17.27%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 2.20-2.42 and 2.54-2.72 (each 1H, each m, CH<sub>2</sub>), 3.00 and 3.02 (total 3H, each s, Me), 3.16-3.42, 3.56-3.62, 3.72-3.76, 3.82-3.94 and 3.98-4.10 (total 5H, each m, 2 of CH<sub>2</sub> and CH), 5.52 (2H, s, CH<sub>2</sub>), 7.22 and 7.24

82

(total 1H, each s, Ar-H), 7.34 (1H, d, J = 8.6Hz, Ar-H), 7.52 (1H, d, J = 8.6Hz, Ar-H), 7.66 (1H, s, Ar-H), 8.06 (1H, s, Ar-H), 8.58 (1H, s, Ar-H).

5 Cl

EXAMPLE 36

8 N-Methyl-3-[5-imidazol-1-ylmethyl-1H-indol-3-yl]pyrrolidine. Oxalate. Hemihydrate

10  $\rho$  Prepared from N-benzyl-3-(formylmethyl)pyrrolidine and 4-(imidazol-1-ylmethyl)phenyl hydrazine hydrochloride as described for Examples 26 and 27. The oxalate hemihydrate  
14 salt was prepared, mp 101-104°C (isopropyl alcohol/Et<sub>2</sub>O);  
(Found: C, 59.51; H, 6.35; N, 14.54.  
15  $C_{17}H_{20}N_4.C_2H_2O_4.0.6H_2O$ . 0.1 (<sup>1</sup>PrOH) requires C, 59.86; H,  
14 6.25; N, 14.47%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O)  $\delta$  2.26-2.42 (1H, m, CH of CH<sub>2</sub>), 2.60-2.74 (1H, m, CH of CH<sub>2</sub>), 3.03 (3H, s, Me), 3.16-4.12 (5H, br m, 2 of CH<sub>2</sub> and CH), 5.45 (3H, s, Me), 7.27 (1H, dd, J = 1.6 and 8.5Hz, Ar-H), 7.31 (1H, s, Ar-H), 7.38-7.40 (2H, m, Ar-H), 7.58 (1H, d, J = 8.5Hz, Ar-H), 7.70 (1H, s, Ar-H),  
20 8.39 (1H, s, Ar-H).

Cl

EXAMPLE 37

25 8 N,N-Dimethyl-2-[5-(2-aminoimidazol-1-yl)-1H-indol-3-yl]ethylamine. Bisoxalate

$\rho$  Prepared from 2-aminoimidazole and 4-fluoro nitrobenzene

as described for Example 16. To prevent reaction of the aminoimidazole with sodium nitrite under the diazotization conditions the amino was protected as the acetamide with  $\text{Ac}_2\text{O}/\text{AcOH}$  prior to hydrogenation and hydrazine formation.

5    8 Fischer reaction of 4-[2-(methylcarbonylamino)imidazol-1-yl]phenyl hydrazine with N,N-dimethylaminobutanal dimethylacetal gave the title-product. The bisoxalate salt was  
14    prepared, mp 199-200°C (MeOH/Et<sub>2</sub>O); (Found: C, 50.35; H, 5.06; N, 15.05. C<sub>15</sub>H<sub>19</sub>N<sub>5</sub>.2.1(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>) requires C, 50.31; H, 10    5.10; N, 15.28%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O)  $\delta$  2.91 (6H, s, N(Me)<sub>2</sub>), 3.27 (2H, t, J = 7.4Hz, CH<sub>2</sub>), 3.50 (2H, t, J = 7.4Hz, CH<sub>2</sub>), 6.97 (2H, s, Ar-H), 7.29 (1H, dd, J = 1.8 and 8.7Hz, Ar-H), 7.48 (1H, s, Ar-H), 7.67 (1H, d, J = 8.7Hz, Ar-H), 7.78 (1H, d, J = 1.8Hz, Ar-H).

15

Cl

EXAMPLE 38

8    N,N-Dimethyl-2-[5-(2-aminoimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Sesquioxalate

20

9    1. 4-Cyanophenylhydrazine. Hydrochloride

25

1    To a cooled (-15°C) and stirred suspension of 4-aminobenzonitrile (50g, 423mmol) in concentrated hydrochloric acid (550ml) was added dropwise a solution of sodium nitrite (31.5g, 457mmol) in water (200ml) at such a rate as to maintain 31    the temperature below -10°C. After the addition was finished,

the reaction mixture was quickly filtered to remove solids and  
31 the filtrate was added portionwise to a cooled (-20°C) and stirred  
solution of tin (II) chloride dihydrate (477g, 2.1mol) in  
concentrated hydrochloric acid (370ml) at such a rate as to  
5 31 maintain the temperature below -10°C. After further 15  
1 minutes at -10 to 0°C, the white precipitate was collected by  
33 filtration, washed with diethyl ether (4 x 250ml) and dried to  
give 56g (78%) of the title compound; mp 235-237°C (ethanol-  
47 water 1:1); <sup>1</sup>H NMR (250MHz, DMSO-d<sub>6</sub>) δ 10.50 (3H, br s,  
10 <sup>13</sup>-N<sup>+</sup>H<sub>3</sub>), 9.10 (1H, br s, <sup>13</sup>-NH-), 7.71 (2H, d, J = 8.8Hz, Ar-H), 7.03  
13 (2H, d, J = 8.8Hz, Ar-H); m/z (CI) 132 (M<sup>+</sup>-1).  
31

P 8 9 2. 2-[5-Cyano-1H-indol-3-yl]ethylamine. Hydrochloride

15 P To a stirred suspension of 4-cyanophenylhydrazine (50g) in  
a mixture of ethanol and water (5:1; 21) was added 47  
chlorobutanal dimethylacetal (45g) and the resulting mixture  
was refluxed for 18 hours. Solvents were removed under  
vacuum and the residue was azeotroped with toluene to give a  
20 brown solid. Crystallisation of this crude material from  
methanol (150ml) gave 23g (35%) of the title compound as a  
47 yellow solid; mp 270-274°C; <sup>1</sup>H NMR (250MHz, DMSO-d<sub>6</sub>) δ  
11.60 (1H, br s, indole N-H), 8.17 (1H, d, J = 1.1Hz, Ar-H), 7.97  
(3H, br s, <sup>13</sup>-N<sup>+</sup>H<sub>3</sub>), 7.54 (1H, d, J = 8.5Hz, Ar-H), 7.46 (1H, s, Ar-  
25 H), 7.44 (1H, dd, J = 8.5 and 1.1Hz, Ar-H), 3.05 (4H, br s,  
-CH<sub>2</sub>CH<sub>2</sub>N-); m/z (CI) 184 (M<sup>+</sup>-1).  
13 31

P8

3. N-tert-Butyloxycarbonyl-2-[5-cyano-1H-indol-3-yl]ethylamine.

P

5 The title compound was prepared in 58% yield from the preceding tryptamine using the conditions described for Example 1 (Step 4); white solid; mp 132-134°C (hexane-ethyl acetate); <sup>1</sup>H NMR (250MHz, CDCl<sub>3</sub>) δ 8.42 (1H, br s, indole N-H), 7.93 (1H, s, Ar-H), 7.41 (2H, s, Ar-H), 7.12 (1H, d, J = 2.2Hz, Ar-H), 4.71 (1H, br s, -NH-), 3.44 (2H, q, J = 6.9Hz, -CH<sub>2</sub>NH-), 10 2.94 (2H, t, J = 6.9Hz, Ar-CH<sub>2</sub>-), 1.45 (9H, s, t-Bu); m/z (CI) 286 (M<sup>+</sup>+1).

P8

4. N-tert-Butyloxycarbonyl-2-[5-aminomethyl-1H-indol-3-yl]ethylamine.

15

P A solution of the product from the previous step (11.3g) in a mixture of absolute ethanol (750ml) and chloroform (22ml) was hydrogenated at 50 psi over platinum (IV) oxide (1g) for 28 hours. The catalyst was removed by filtration and solvents were removed under vacuum. Flash chromatography of the residue (silica gel, dichloromethane-methanol-ammonia 90:10:1) gave 14 9.5g (82%) of the title compound as a white solid; mp 147-149°C; 17 <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 8.04 (1H, br s, indole N-H), 7.52 (1H, s, Ar-H), 7.33 (1H, d, J = 8.4Hz, Ar-H), 7.16 (1H, d, J = 25 UMS 8.4Hz, Ar-H), 7.03 (1H, s, Ar-H), 4.61 (1H, br s, -NHBOC), 3.96 L (2H, s, Ar-CH<sub>2</sub>NH<sub>2</sub>), 3.45 (2H, br q, -CH<sub>2</sub>NHBOC), 2.95 (2H, t, J = 6.8Hz, Ar-CH<sub>2</sub>-), 1.43 (9H, s, t-Bu); m/z (CI) 288 (M<sup>+</sup>-1).

31

86

P 8

9

5. N-tert-Butyloxycarbonyl-2-[5-dimethylaminomethyl-1H-indol-3-yl]ethylamine.

P

5 The title compound was prepared in 71% yield from the product from the previous step using the conditions described for Example 3 (Step 3); colourless thick oil;  $^1\text{H}$  NMR (250MHz,  $\text{CDCl}_3$ )  $\delta$  8.07 (1H, br s, indole N-H), 7.50 (1H, s, Ar-H), 7.31 (1H, d,  $J$  = 8.3Hz, Ar-H), 7.16 (1H, d,  $J$  = 8.3Hz, Ar-H), 7.02 (1H, s, Ar-H), 4.61 (1H, br s,  $-\text{NH}-$ ), 3.54 (2H, s, Ar- $\text{CH}_2\text{N}-$ ), 3.45 (2H, q,  $J$  = 6.2Hz,  $-\text{CH}_2\text{NH}-$ ), 2.94 (2H, t,  $J$  = 6.2Hz, Ar- $\text{CH}_2-$ ), 2.27 (6H, s,  $-\text{NMe}_2$ ), 1.43 (9H, s, t-Bu).

P 8

9

15 6. N-tert-Butyloxycarbonyl-2-[5-trimethylammonium methyl-1H-indol-3-yl]ethylamine. Iodide

15

P A solution of the product from step 5 (2.9g) in a mixture of anhydrous diethyl ether (170ml) and iodomethane (36ml) was allowed to stand at room temperature for 16 hours in the dark. The white solid was collected by filtration, washed with diethyl ether and dried over phosphorous pentoxide at 50°C under 14 vacuum to give 4.2g (100%) of the title compound; mp 199-202°C (decomposition);  $^1\text{H}$  NMR (360MHz,  $\text{DMSO-d}_6$ )  $\delta$  11.09 (1H, br s, indole N-H), 7.69 (1H, s, Ar-H), 7.44 (1H, d,  $J$  = 8.3Hz, Ar-H), 7.26 (1H, s, Ar-H), 7.19 (1H, d,  $J$  = 8.3Hz, Ar-H), 6.89 (1H, br t,  $-\text{NH}-$ ), 4.57 (2H, s, Ar- $\text{CH}_2\text{N}-$ ), 3.23 (2H, q,  $J$  = 7.6Hz,  $-\text{CH}_2\text{NH}-$ ), 3.01 (9H, s,  $-\text{N}^+\text{Me}_3$ ), 2.83 (2H, t,  $J$  = 7.6Hz, Ar- $\text{CH}_2-$ ), 1.37 (9H, s, t-Bu); m/z (FAB) 332. (Found: C, 49.30; 25 13

H, 6.55; N, 8.79.  $C_{19}H_{30}IN_3O_2$  requires: C, 49.68; H, 6.58; N, 9.15%).

P 8

5 9

7. N-tert-Butyloxycarbonyl-2-[5-(2-nitroimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine.

P      Sodium hydride (0.6g of a 60% dispersion in oil) was added to a stirred solution of 2-nitroimidazole (1.61g, 14.2mmol) in DMF (65ml), at room temperature. After 0.5h, a solution of the preceding methiodide (3.26g, 7.1mmol) in DMF (40ml) was added and the mixture refluxed for 2h and then stirred at room temperature for 18h. Aqueous work-up followed by flash chromatography of the crude product, afforded the title compound (2.6g);  $^1H$  NMR (360MHz,  $CDCl_3$ )  $\delta$  1.43 (9H, s, t-Bu), 2.94 (2H, t,  $J$  = 7.0Hz,  $CH_2$ ), 3.40-3.48 (2H, m,  $CH_2$ ), 5.69 (2H, s,  $CH_2$ ), 7.01 (1H, s, Ar-H), 7.09 (1H, d,  $J$  = 8.4Hz, Ar-H), 7.10 (2H, s, Ar-H), 7.37 (1H, d,  $J$  = 8.4Hz, Ar-H), 7.54 (1H, s, Ar-H), 8.12 (1H, s, indole-NH).

20 P 8

9

8. 2-[5-(2-Nitroimidazol-1-ylmethyl)-1H-indol-3-yl]ethylamine.

25

P      A solution of the preceding imidazole (2.6g, 6.7mmol) in 90%  $HCO_2H$  (150ml) was stirred at room temperature for 1.25h. The reaction was quenched by addition of MeOH and the solvents removed under vacuum. The crude product was purified by flash chromatography on silica-gel eluting with

$\text{CH}_2\text{Cl}_2/\text{EtOH}/\text{NH}_3$  (30:8:1). The product (0.73g) was obtained as a yellow oil;  $^1\text{H}$  NMR (360MHz,  $d_4$ -MeOH)  $\delta$  2.87-2.94 (4H, m, 2 of  $\text{CH}_2$ ), 5.71 (2H, s,  $\text{CH}_2$ ), 7.05 (1H, d,  $J$  = 8.4Hz, Ar-H), 7.11 (1H, s, Ar-H), 7.12 (1H, s, Ar-H), 7.35 (1H, d,  $J$  = 8.4Hz, Ar-H), 7.39 (1H, s, Ar-H), 7.55 (1H, s, Ar-H).

### 9. N,N-Dimethyl-2-[5-(2-nitroimidazol-1-ylmethyl)-1H-*o*

### 9 indol-3-yllethylamine.

10       $\textcircled{P}$       Prepared from the preceding tryptamine using the  
 conditions described for Example 3(Step 3);  $^1\text{H}$  NMR (250MHz,  
 $\text{CDCl}_3$ )  $\delta$  2.33 (6H, s,  $\text{N}(\text{Me})_2$ ), 2.62 (2H, t,  $J$  = 7.4Hz,  $\text{CH}_2$ ), 2.92  
 (2H, t,  $J$  = 7.4Hz,  $\text{CH}_2$ ), 5.68 (2H, s,  $\text{CH}_2$ ), 7.00 (1H, d,  $J$  =  
 1.0Hz, Ar-H), 7.07 (1H, dd,  $J$  = 1.0 and 8.2Hz, Ar-H), 7.09 (1H, d,  
 15       $J$  = 2.4Hz, Ar-H), 7.10 (1H, d,  $J$  = 2.4Hz, Ar-H), 7.35 (1H, d,  $J$  =  
 8.2Hz, Ar-H), 7.53 (1H, s, Ar-H), 8.19 (1H, br s, indole-NH).

#### 10. N,N-Dimethyl-2-[5-(2-aminoimidazol-1ylmethyl)-1H-*c*]

### indol-3-ylmethylamine. Sesquioxalate

20      The title-compound was prepared from the product of Step  
 9 using the conditions described for Example 5 (Step 2). The  
 14 sesquioxalate salt was prepared, mp 211-212°C (MeOH/Et<sub>2</sub>O);  
 ( Found: C, 54.46; H, 6.08; N, 16.53.  
 25      C<sub>16</sub>H<sub>21</sub>N<sub>5</sub>.1.5(C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>).0.06 (MeOH) requires C, 54.46; H,  
 6.75; N, 16.66%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 2.91 (6H, s,  
 N(Me)<sub>2</sub>), 3.25 (2H, t, J = 7.4Hz, CH<sub>2</sub>), 3.49 (2H, t, J = 7.4Hz,

CH<sub>2</sub>), 5.16 (2H, s, CH<sub>2</sub>), 6.77 (1H, d, J = 2.3Hz, Ar-H), 6.83 (1H, d, J = 2.3Hz, Ar-H), 7.19 (1H, dd, J = 1.5 and 8.5Hz, Ar-H), 7.39 (1H, s, Ar-H), 7.56 (1H, d, J = 8.5Hz, Ar-H), 7.61 (1H, s, Ar-H).

5 Cl  
|  
8

EXAMPLE 39

8 N-Methyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

10 P 8 1. N-Benzyl-2[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine.

P 8 To a solution of 2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine (1.5g, 6.2mmol) in EtOH (30ml) was added freshly 9  
15 distilled benzaldehyde (0.66g, 6.2mmol) and the solution stirred at room temperature for 21h. NaBH<sub>4</sub> (0.24g, 6.3mmol) was added portionwise over 10 min, at room temperature, and the resulting mixture was stirred for 0.5h before the solvent was removed under vacuum. The resulting residue was taken up 20 into water (10ml) and acidified with 1N HCl (15ml). The mixture was then basified with 2N NaOH and extracted with 33 EtOAc (4 x 50ml). The combined organic phases were washed with brine (30ml), dried and concentrated. Chromatography of the residue on silica-gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/MeOH (85:15) 25 gave the title-product (1.38g, 67%); <sup>1</sup>H NMR (360MHz, CDCl<sub>3</sub>) δ 2.94 (4H, s, 2 of CH<sub>2</sub>), 3.80 (2H, s, CH<sub>2</sub>), 5.38 (2H, s, CH<sub>2</sub>), 7.04

(1H, d,  $J = 2$ Hz, Ar-H), 7.08 (1H, dd,  $J = 1.5$  and  $8.4$ Hz, Ar-H),  
7.18-7.30 (5H, m, Ar-H), 7.32 (1H, d,  $J = 8.4$ Hz, Ar-H), 7.54 (1H,  
s, Ar-H), 7.94 (1H, d,  $J = 2$ Hz, Ar-H), 8.17 (1H, br s, indole-NH).

ρ 5 8        2. N-Benzyl-N-methyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine.  
9

ρ        To a stirred solution of the preceding amine (1.14g,  
3.4mmol) in anhydrous DMF (45ml) was added  $K_2CO_3$  (0.89g,  
6.4mmol) and dimethyl sulphate (0.46g, 3.7mmol). The mixture  
10      was stirred at room temperature for 3.5h before adding  $H_2O$   
33      (90ml) and extracting with EtOAc (2 x 100ml). The combined  
organic solutions were washed with brine (40ml), dried, and  
concentrated. The residue was chromatographed on silica-gel  
15      eluting with  $CH_2Cl_2/MeOH$  (90:10) to give the desired product  
47/14 (0.69g);  $^1H$  NMR (360MHz,  $CDCl_3$ )  $\delta$  2.34 (3H, s,  $CH_3$ ), 2.70-  
2.76 (2H, m,  $CH_2$ ), 2.94-3.00 (2H, m,  $CH_2$ ), 3.60 (2H, s,  $CH_2$ ),  
5.38 (2H, s,  $CH_2$ ), 7.04 (1H, d,  $J = 2$ Hz, Ar-H), 7.08 (1H, dd,  $J =$   
2 and  $8.4$ Hz, Ar-H), 7.20-7.36 (6H, m, Ar-H), 7.44 (1H, s, Ar-H),  
20      7.94 (1H, s, Ar-H), 7.96 (1H, s, Ar-H), 8.18 (1H, br s, indole-NH).

P 8

3. N-Methyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

P A solution of the preceding benzylamine (0.69g, 2.0mmol) in ethanol (100ml) and 2N HCl (2ml) was hydrogenated at 30 psi over 10% Pd/C (0.6g) for 4h. The catalyst was removed by filtration through hyflo, the solvent removed under vacuum, and the residue chromatographed on silica-gel eluting with CH<sub>2</sub>Cl<sub>2</sub>/EtOH/NH<sub>3</sub> (40:8:1) to give the title-N-methylamine (0.34g, 68%). The oxalate salt was prepared and recrystallised from isopropyl alcohol; mp 149-150°C; (Found: C, 55.42; H, 5.72; N, 19.55. C<sub>14</sub>H<sub>17</sub>N<sub>5</sub>.C<sub>2</sub>H<sub>2</sub>O<sub>4</sub>.0.15 (iPA) requires C, 55.72; H, 5.75; N, 19.76%); <sup>1</sup>H NMR (360MHz, D<sub>2</sub>O) δ 2.44 (3H, s, CH<sub>3</sub>), 2.87-2.98 (4H, m, 2 of CH<sub>2</sub>), 5.41 (2H, s, CH<sub>2</sub>), 7.05 (1H, s, Ar-H), 7.09 (1H, dd, J = 1.6 and 8.4Hz, Ar-H), 7.31 (1H, d, J = 8.4Hz, Ar-H), 7.57 (1H, s, Ar-H), 7.96 (1H, s, Ar-H), 7.99 (1H, s, Ar-H).

Cl

EXAMPLE 40

20



Tablet Preparation

P 25

Tablets containing 1.0, 2.0, 25.0, 26.0, 50.0 and 100.0mg, respectively of the following compounds are prepared as illustrated below:

92

[ ]  
8 9

- 92 -

T1092Y

PO N,N-Dimethyl-2-[5-(2-methyltetrazol-5-ylmethyl)-1H-indol-3-yl]ethylamine. Oxalate.

5 PO N,N-Dimethyl-2-[5-(1,2,4-triazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Benzoate.

PO N,N-Dimethyl-2-[5-(1,2,3,4-tetrazol-1-ylmethyl)-1H-indol-3-yl]ethylamine. Succinate.

10 PO N-Methyl-4-[5-imidazol-1-yl-1H-indol-3-yl]piperidine. Sesquioxalate.

PO N-Methyl-3-[5-(1,2,3-triazol-1-yl)-1H-indol-3-yl]pyrrolidine. Oxalate.

15

T930X TABLE FOR DOSES CONTAINING FROM  
1-25MG OF THE ACTIVE COMPOUND

20

	Amount-mg		
Active Compound	1.0	2.0	25.0
Microcrystalline cellulose	49.25	48.75	37.25
Modified food corn starch	49.25	48.75	37.25
Magnesium stearate	0.50	0.50	0.50

25

93

T940X

TABLE FOR DOSES CONTAINING FROM  
26-100MG OF THE ACTIVE COMPOUND

5

	Amount-mg		
Active Compound	26.0	50.0	100.0
Microcrystalline cellulose	52.0	100.0	200.0
Modified food corn starch	2.21	4.25	8.5
Magnesium stearate	0.39	0.75	1.5

10

P All of the active compound, cellulose, and a portion of the corn starch are mixed and granulated to 10% corn starch paste. The resulting granulation is sieved, dried and blended with the remainder of the corn starch and the magnesium stearate. The resulting granulation is then compressed into tablets containing 1.0mg, 2.0mg, 25.0mg, 26.0mg, 50.0mg and 100mg of the active ingredient per tablet.

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